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Section on Pathology and Physiology,
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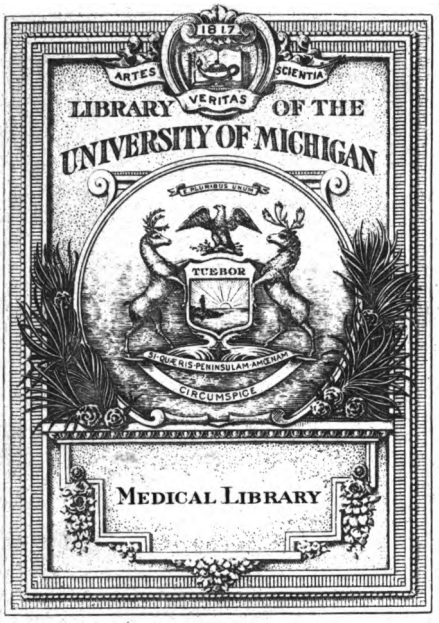

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TRANSACTIONS OF THE

SECTION ON

PATHOLOGY AND PHYSIOLOGY

of the
American Medical Association
at the Fifty-ninth Annual
Session, held in Chicago,
Illinois, June 2 to 5, 1908

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THE OPPOSITION TO MEDICAL RESEARCH.

CHAIRMAN'S ADDRESS IN THE SECTION ON PATHOLOGY, AND PHYSIOLOGY, AMERICAN MEDICAL ASSOCIATION, JUNE 5-8, 1908.

W. B. CANNON, A.M., M.D.
George Higginson Professor of Physiology in Harvard Medical School.
BOSTON.

In several states during the past year there has been vigorous agitation for legislative restriction of the use of animals for medical research. This agitation is not new. For many years in Massachusetts petitioners have appealed for laws controlling laboratory methods, and previous attempts to secure such laws have been made also in Illinois, Pennsylvania and New York. In England, where a restrictive act has been enforced since 1876, still more drastic law is now demanded.

To those who are active in promoting medical science, the experience of England is particularly instructive, because the legislation asked for in this country is largely based on the English act of 1876. This act is pointed to as a model. But the present appeal in England for more drastic law indicates that even were the English act transferred to our statutes, it would be merely initial and temporary, and that it would not be permanently satisfactory to many of the agitators. Indeed, both individuals and societies hostile to the laboratories have clearly stated that what they desire is total abolition of animal experiments, and that restrictive legislation is the first step to that end. The prospect, therefore, is toward an indefinitely extended struggle for the legislative control of the methods of medical research.

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The controversy is one in which violent emotions have been aroused. In some instances the attack on scientific methods has been forced with unmitigated bitterness. Under such conditions each side is prone to be blindly unjust to the other. Until the contestants can meet each other fairly and dispassionately, the controversy can never be limited to the merits of the opposed causes. It must always involve irrelevant personalities. Is it not, therefore, of prime importance to inquire into the reasons for the unfair and irritating misconceptions which prevail? So it seemed to me; and I propose to consider some of these reasons, such as the conflict of testimony, the experience and characteristics of the contestants, certain assumptions regarding animals, and the questions of motive.

THE CONFLICTING STATEMENTS AS TO PAINFUL EXPERIMENTS.

The use of animals for experimental purposes is commonly called "vivisection." It is an unfortunate word, because it has come to have various meanings which are not clearly distinguished. To the "antivivisectionist" the word vivisection too frequently signifies the cutting or dissection of sentient living animals, bound or restrained, and subjected to the full torture of extensive operation without anesthesia. The repeated tales of cruelty, the illustrations of instruments used in laboratory service, and the imaginary pictures of the sufferings which animals are supposed to endure at the hands of the experimenter, indicate the hideous significance ordinarily attached to the word vivisection. To the medical investigator, on the contrary, the word means something quite different. It means, to be sure, operations on living animals, but it does not imply attendant pain. If an animal is anesthetized, and operated on, and is killed without recovery from anesthesia, evidently the operation has not caused pain to the animal. So far as the experience of the animal is concerned, the

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operation would not have been different in effect, if the animal had first been killed, and later dissected. Now it has been shown repeatedly that in almost all physiologic experiments the observations of the living processes are made in precisely this way, i. e., while the animals are on the way to death by anesthesia. In pathologic and bacteriologic investigation injections are made and sometimes diseases are produced; and in surgical research it is occasionally necesssary, after a painless operation, to keep the animals alive in order to observe the effects of the surgical procedure. It is probable, in these instances of inoculation and aseptic operation, that the animals feel ill, as they do with a distemper. Even if the lower animals were as sensitive as man, the pain, if we may judge from human experience, would not be great. There is abundant evidence, however, that the lower animals are not so sensitive as man. And, furthermore, these bacteriologic and surgical experiments are precisely the experiments which bear most directly on the explanation and the cure of disease in the much more sensitive organism, the human being.

In an inquiry made some years ago, Dr. C. F. Hodge found that of nearly 1,700 animals (including 866 frogs) used for experimental purposes in Massachusetts in one year, the operations in 64 per cent. were painless; in 12.2 per cent, as painful as vaccination; in 0.4 per cent. as painful as the healing of a wound; in 1.6 per cent. as painful as the effect of poison, and in 21.8 per cent. as painful as disease.[1] The official figures for Great Britain for 1906, are as follows:

	Per cent.
Inoculations or similar methods not involving any operation	93.96
Animals killed under anesthetic	3.10
Animals killed under anesthetic after a demonstration	0.34
Animals allowed to recover from anesthetic (no observation or stimulation likely to cause pain and no further operative procedure allowed without anesthetic)	2.60
	100.00

1. Pop. Sc. Month., 1896, xlix, 783.

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Since the pain of inoculation is trifling, and since in the vast majority of operations even on human beings the aseptic healing of wounds causes no considerable pain after full recovery from the anesthetic,[2] and since much of the suffering from disease is due to the anxiety for friends or relatives rather than to physical distress, the total body of pain resulting from animal experimentation is in all antivivisection literature grossly exaggerated.

It has been estimated that not more than 1 per cent. of the experimental procedures are really painful. As a physiologist, Hodge has testified that in more than ten years' experience in various laboratories in this country and abroad he had never had occasion to perform or witness an experiment of this painful class. I can testify to the same experience in my own career of twelve years as medical student and physiologist. And Professor Starling, writing of the use of dogs for research, states that though he has been engaged in the experimental pursuit of physiology for the last seventeen years, on no occasion has he seen pain inflicted on a dog or cat in any physiologic laboratory in England.

In opposition to this testimony as to the practically painless character of the immense majority of operations in experimental medicine, are the statements found on all sides in the writings of antivivisectionists. Some of these cases are records of experiments performed more than sixty years ago, before the use of anesthetics; some of them are frankly of the class of experiments involving pain or discomfort; and some of them are clear instances of misinterpretation by persons too unfamiliar with animal functions and the action of anesthetics to understand ordinary physiologic description. On the assumption that no one concerned in this discussion desires to imply an untruth, it is evident that the failure

2. M. H. Richardson, Animal Experimentation, p. 53. Boston, 1902.

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to recognize the extremely small percentage of cases involving pain, when such cases are cited, is clearly misleading. The failure to discriminate between the various sorts of experiments, the diffusion of the impression that animal experiments are almost uniformly attended with extremes of suffering, the neglect of the great accumulation of fact that testifies to the splendid results of medical research, the monotonous repetition of the hostile opinions of a few physicians long since dead—these characteristics of the attacks on medical investigators lead to the inference that the agitators for legislation are not as devoted as they should be to the spirit of fair play.

The belief that there is great suffering among animals used for experimental purposes is based to a large extent on a refusal to accept the statements of the experimenters. "The vivisectionist anesthesia I have no confidence in, and my association has no confidence in,"[3] such is the characteristic attitude of the opponents of animal experimentation. "I think that all these experimenters have the greatest contempt for the Act of Parliament,"[4] these are the words with which the honorary secretary of the National Antivivisection Society of England expresses his belief that English investigators do not hesitate to inflict pain in defiance of the law. Indeed, he states further, "The knowledge that horrible mutilations may be daily and hourly executed on the bodies of living creatures with no adequate security for their insensibility makes very many humane people profoundly miserable, it rises day and night between them and their peace of minds, it haunts their lives waking and asleep, it deprives them of joy in this world which otherwise might be theirs."[5] From

3. Testimony of Mrs. K. Cook, Appendix to First Report of the Royal Commission on Vivisection, October to December, 1906, p. 72.

4. Testimony of Hon. S. Coleridge, Appendix of the Third Report of the Royal Commission on Vivisection. April to July, 1907, p. 183.

5. Ibid., p. 146.

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what may be found in the writings of other antivivisectionists this implication of secret atrocities in laboratories would be widely accepted as highly probable.

In no feature of the controversy is the difference between the opposing parties more clearly marked than in this attitude regarding the experience of the animals at the hands of investigators. The investigators state that they know nothing of the tortures and horrible cruelties that have been imagined; indeed, that the vast majority of operations are practically painless. The critics, on the other hand, are not only suspicious of the experimenter and distrustful of his testimony, but have even ventured to make accusation of deliberate lying. In any such conflict of testimony it is desirable to inquire into the qualifications of the witnesses in order that a proper estimate may be placed on the opposing statements.

QUALIFICATIONS FOR TESTIFYING.

The reason for distrusting the word of medical investigators is not evident. In almost all instances these men are trained scholars; in many instances they are also practitioners of medicine in whom members of the community place supreme confidence. As men of science their service to their fellow men consists in the search for new truth. In this process of discovery their eyes and ears are especially exercised in exact observation. their minds are continually disciplined to draw only justifiable inferences from what they have observed. They are, therefore, well qualified to report regarding the events which occur in laboratories.

In reporting their experiments it is of the greatest importance, in the interest of truth, that investigators state precisely the details of the procedure ,and the results that were secured. Every new investigation is a venture into the unknown from regions already known, —an extension of previous knowledge. It is the duty of investigators in their reports to give credit to those

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who secured the previous knowledge. They are, therefore, accustomed to study the original records of investigation, and to make exact reference to the words on which their own statements are based.

That men of science are infallible, I do not for a moment contend. But I maintain that the search for what is true, and the exact reporting of what is found, are the ideals which animate the lives of scientific investigators, and that the pursuit of these ideals is excellent training in telling the truth.

In examining the qualifications of antivivisectionists to bear reliable testimony against the methods of medical research, it is first necessary to consider the sorts of persons that are to be found among them. If one may judge from representatives at legislative hearings and from names on petitions, the opponents of research consist of many women, fewer clergymen, lawyers, artists and business men, and a relatively very small number of physicians. Setting aside for the moment the physicians who sign petitions for restrictive legislation, and considering the other opponents of medical research, one notes that they are persons without training in the methods of biologic investigation. They do not enter the laboratories in which they declare animals are cruelly tortured, they do not see the operations they criticise, they do not realize that there are various degrees of anesthesia (used by surgeons in operations on man), they do not know enough of the history of the medical sciences to judge the great contributions which experiments on animals have given to practical medicine and surgery, they are unacquainted with the dire problems still presented by diseases which continue to kill their thousands and tens of thousands. With all this lack of positive qualification for passing judgment on the work of the investigator there is commonly combined a keen sensibility and a vivid imagination.

Precisely this combination of real ignorance with unchecked imagination causes most of the difficulty.

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Imagination is permitted to take the place of careful inquiry. The tormenting of animals is assumed to prevail in medical laboratories, with no adequate proof that such is the case. Dark suspicions and insinuations are suggested against honorable men whose lives are devoted through research to the relief of human ills. Absurd claims and grotesque misinterpretations result from this eager fancy allowed free play in reading the records of experiments. Commenting on an experiment in which the peripheral end of a nerve, which had been severed under ether, was stimulated, Mr. P. G. Peabody stated, "It will be readily seen, even by the casual reader, that it involves an amount of agony beyond which science is unable to go and to approximate to which is impossible except by a person who has devoted long years to the study of nerves."[6] The casual layman may indeed be impressed by this apparently authoritative declaration that here is a case of atrocious cruelty; but the most primitive acquaintance with the nature of nervous conduction would have shown the utter absurdity of the assumption that even the slightest pain could have been inflicted by stimulating a piece of nerve separated from the central nervous system. This case is merely an example of many similar cases that might be cited.

Not only are most antivivisectionists, because of ignorance, incapable of intelligent interpretation of the records of experiments, they are also too frequently lacking in those scholarly qualities which demand accuracy of reference and exactness of quotation. Some years ago Dr. W. W. Keen published a large number of examples from antivivisection literature, in which the references were vague, inaccurate or garbled, and in some instances showed extraordinary and repeated interpolations and mistranslations.[7] Only last year there appeared an essay against vivisection, in which experi-

6. Leaflet published by the N. E. Antivivisection Society.
7. THE JOURNAL A. M. A., 1901, xxxvi, 500.

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ments performed under anesthesia are quoted as evidence of horrible cruelty, an experiment never performed at all is cited to show the callousness of the investigator, and arguments and statements which have been clearly answered or qualified, are repeated in their original form, as if they expressed the exact truth. This essay was granted a prize of $300, by a committee of anti-vivisectionists. Its author declares that the object of her article is "not to bandy words with professional and learned men," but to state simply "some thoroughly authenticated facts."[8]

Here, then, are the opposed parties; on the one side men trained to close observation, to careful inference, and to exact statement; on the other side persons revealing repeatedly that they are ignorant of the subject they denounce, that they are incapable of interpreting intelligently what they read, and that they let imagination play uncontrolled in regions they have never visited and in procedures they have never witnessed. These two parties can never be reconciled until both have the same desire to know the truth, and the same willingness to search for it with clear eyes and unbiased mind.

THE COMPLEX RELATIONS BETWEEN RESEARCH AND MEDICAL AND SURGICAL PRACTICE.

As already stated, the men engaged in research in the medical sciences are trained investigators. Most of them have had a long course in medicine, and after that they have had specialized experience in their chosen field of labor. They are engaged in a study of by far the most complicated structures and the most complicated processes in nature, the structures and processes of highly developed animals. And not only are the individual processes intricate, but the animals themselves are intricately related in the nexus of living beings. So complex are the relations that in the fight against disease an immediate and fundamental answer to the urgent

8. Britton: Our Dumb Animals, 1908, xl, 121.

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practical problem is usually impossible. Each problem must be analyzed into smaller and simpler problems, and these must be patiently investigated, one by one, before the results can be combined into a solution of the practical difficulty.

Thus the question of the proper method of checking the spread of tuberculosis depends primarily on a knowledge of how the disease is spread, and that knowledge, in turn, depends on a knowledge of the cause of the disease, and that depends on a study of tuberculous tissues, and the discovery that in these tissues are bacilli, and the demonstration that these bacilli when separated in pure state and injected by themselves into animals, will produce the disease tuberculosis; and from this point the dependence runs back in all directions—to the discovery of the microscope and its perfection, to the methods of histologic investigation and the use of staining reagents, to suggestions from the study of alcoholic, lactic and acetic fermentations, to the laborious first proof that infectious diseases result from micro-organisms, and to innumerable other factors, which at every step determined whether or not progress could be made. By the failure of any one of this complex group of factors the development of our present methods of dealing practically with the spread of tuberculosis might have been stopped absolutely.

This sketch of the development of our intelligence regarding tuberculosis is only a fair example of the intricate interweaving of knowledge. If all the bearings of every discovery could be at once ascertained, or if every investigator could foresee where his advance would be delayed by ignorance in closely related fields, it might be possible to move forward with greater directness. But these conditions are impossible. The relations are too intricate. Knowledge has to be pieced together after slow and tedious labor in small realms of fact. Yet though the realm any man explores must be small and limited, he has the assurance that just in so

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far as he sees clearly and tells exactly what he sees, his contribution will fit in with other contributions and thus will find its value in the growing body of truth.

Yellow fever has practically been abolished in Cuba where it was a devastating disease and a constant menace to our southern cities. The glory of that service has justly been bestowed on the army surgeons who proved the manner in which the disease is conveyed from one person to another. It should not be forgotten, however, that the beneficent results of their work were due in part to the entomologists who had previously studied the veins and scales on the wings, and the hairs and scales on the bodies of mosquitoes, and had observed the ways in which mosquitoes reproduce. Surely these studies appear remote enough from the great human problems of disease and death. Yet how closely are they involved!

This complexity of the relation between discoveries and practice has important bearings in the present discussion of the opposition to medical research. It is the certainty that we are still wofully ignorant of many of the problems of disease, and that every fragment of biologic knowledge may be useful in solving these problems—it is this certainty, and the sincere conviction that the service he performs is in the highest sense humane, that cause the medical investigator to oppose any attempt to check the freedom of investigation. On the other hand, it is the failure of the inexperienced layman to appreciate the complicated relation between investigation and practice, that causes him to look somewhat scornfully on this or that special study and inquire with some warmth, "What can be the use of that?"

In antivivisection writings this question of utility is frequently asked; it is sometimes answered by the statement that all animal experimentation is worse than useless. And in the popular mind the statement is received unchallenged. No doubt some of the widespread ignorance of the relations between medical re-

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search and its practical bearings exists because the profession has made no attempt to enlighten the public on these matters. But how many physicians are capable of elucidating these complex relations? Certainly their training in most medical schools does not give them any clear notion of the sources of their knowledge. Their authorities are their professors and their textbooks. The urgency of teaching what to do does not always admit teaching the why and wherefore, and how the why and wherefore were discovered. Just as very few of us know the processes through which our common possessions, such as our clothes, for example, must go before they belong to us, so, too, the student of medicine knows little of the years of patient investigation which preceded the results he learns to use in his practice.

Under the circumstances it is not to be wondered at that physicians can be secured to sign petitions for laws restricting medical investigation. The proposed law seems harmless, an eager patient is interested, and the amiable doctor signs. The fact that physicians' names are on the list is regarded as the strongest support of the petitioners. But, again, the inquiry must be made, What do they know about the conditions of medical research? What do they know of its relations to practice?

Do the petitioners for restrictive legislation realize that the entire fundamental conception of infectious diseases was established by Pasteur through experiments on animals, and that all the modern methods of checking these diseases arise from that conception? Do they understand that some of the most important means of early diagnosis, most important not only for the individual but for the community as well, are dependent on the use of animals? Do they know that methods of treatment, of the greatest value, such as are used in rabies and diphtheria, for example, have been determined by animal experimentation? Do they recognize

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the necessity of employing animal tests in assuring pure food and pure water to a community? As physicians or as patients are they aware that in using chloral, sulphonal, trional, cocain, eucain, antipyrin, acetanilid, physostigmin, strophanthus, amyl nitrite, adrenalin, thyroid extract—are they aware that they are using drugs discovered or first demonstrated by observations on animals? I have heard antivivisectionists declare that they would refuse to profit by discoveries made on animals. This declaration shows their profound ignorance of the interdependence of modern medical and surgical practice and modern hygiene, on the results of animal experiments. In our civilization it is impossible to escape from the beneficent results of such experiments. We are surrounded by the protection that animals have afforded us. Even the warnings in the street cars against spitting are there because animal experiments proved that such warnings were necessary for our safety.

The scientific application of the experimental method has transformed the world of commerce and industry. The marvel of that transformation is a story that man tells with a just pride in his own achievement. The same sort of painstaking search for knowledge that gave man control of the forces of inorganic nature, has given him most of the control which he now has over the forces of organic nature. It was the method of experiment applied to animals that wrought the change from the empirical medicine of sixty years ago to such exactness of treatment as modern medicine can utilize. And just as the future growth in the physical world must wait further discoveries and new applications of knowledge, so in the realm of biology and medicine, the hope of progress must rest on a continuation of the method which has brought us thus far out of the darkness of the unknown—it must rest on the study of normal and pathologic processes that go on in living animals.

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ASSUMPTIONS REGARDING ANIMALS.

Of the animals used in medical research those which rouse the greatest feeling are the dog and the cat. Throughout known history these animals have been the companions of man. They are household pets. The dog especially is capable of exhibiting a degree of affection and devotion which calls forth a like affection and devotion from his master. It is characteristic of our ways of thinking that when a general statement is made most of us interpret it in those concrete terms with which we are best acquainted—when the statement is made that dogs and cats are vivisected we are likely to think of our own dog or cat in relation to this possibility. This tendency to conceive general propositions concretely in accordance with personal experience, novelists and story-tellers, with ignorance and imagination, have utilized to harrow the feelings of animal lovers and thus to turn deep-seated sentiment strongly against the methods of medical research.

In every large city the accumulation of stray dogs and cats is a menace to public welfare. These wandering dogs are frequently vicious, they bite one another, they fight and sometimes kill dogs that are well-behaved pets, and in their wanderings they serve to keep existent the dread disease—hydrophobia. These dangers are recognized as community dangers, and instead of all dogs having the right to life, liberty and the pursuit of happiness, which some antivivisectionists imply they should have, stray dogs are collected from the streets and are put to death. In London more than 20,000 dogs are annually suffocated in the lethal chamber. In Boston between 3,000 and 4,000 dogs and between 13,000 and 15,000 cats are killed every year by an endowed organization and by public officials. The records of every large city would tell a similar tale.

The dogs and cats used in medical research are just such animals—stray animals, often bedraggled and vicious, and savage from hunger and neglect, that are

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brought into the laboratories from the streets. In a medical school in which active research is progressing, two or there hundred of these stray animals might be used in a year. During their confinement they are well fed and well cared for.

On their way to death in the laboratories they serve to increase biologic knowledge, knowledge of great value to medicine and surgery; thereby they contribute to the alleviation of human suffering. In the public pound the lives of their wretched fellows go out with no service rendered. It is mere useless death.

There is no question that these thousands of dogs must die. Granted that in almost all cases there is no greater discomfort in the one way to death than in the other, which is the more desirable way for these doomed animals to die—while rendering service to their fellow-creatures, or without benefit to any one? This is the question that should be raised when there is talk of the vivisection of dogs and cats. And I believe that in time an enlightened community will not hesitate to pronounce in favor of the way which renders human service.

THE SIMILARITY OF MOTIVE.

It is the contention of the antivivisectionists that their movement is a crusade against pain. Their opposition to medical research is chiefly based on the belief that pain is commonly inflicted on animals in laboratories to a degree too horrifying to endure. So convinced are they of the existence of torments that they have not hesitated to call laboratory workers "fiends," "demons," "human monsters," "diabolical vivisectors," nor to characterize medical research as a "vile pursuit," "a devilish science," "an inhuman as well as a criminal practice," "an organized system of barbarity." These are merely sample epithets. Believing that these things are true, the opponents of animal experimentation are intent on checking it or abolishing it altogether—with

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this "plague of scientific cruelty" the only cure is to "stamp it out." The medical investigators declare that they, too, are on a great crusade against pain. But they take definite issue with the methods of their opponents.

In the first place, the investigators object to any step tending to check the use of animals in medical research. They maintain that such interference is not justified by the present treatment of the experimental animals. They declare that the imagined horrors of medical research do not exist. The insane lust for blood, the callousness to the infliction of pain, which are attributed to the experimenters, they resent as most absurd and unjust accusations. Only the moral degenerate is capable of inflicting the torments that the anti-vivisectionists imagine. No one who is acquainted with the leaders in medical research, who are responsible for the work done in the laboratories, can believe for a moment that they are moral degenerates.

The medical investigators further maintain that judgment should be based on knowledge, not ignorance. They rightly insist that their critics are ignorant—ignorant of the conditions of medical research and ignorant of the complex relations of the medical sciences to medical and surgical practice. And they contend that these critics in their ignorance are endeavoring to stop that experimental study of physiology and pathology, which, as Osler states, in the half-century between 1850 and 1900, did "more to emancipate medicine from the routine and thraldom of authority than all the work of all the physicians from the days of Hippocrates to Jenner," and he adds, "we are yet but on the threshold."

"We are yet but on the threshold"—that is the center of this controversy. How little we really know of scarlet fever and pneumonia, of diabetes, sclerosis and the cerebral degenerations, of the forms of nephritis, and of cancer! How urgent is the cry for more light on these and on many other human afflictions! This is the fact that drives the investigator to renewed exertions. The

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progress of the past few decades has, indeed, been splendid, but in spite of this progress problems of immense importance to the health and the saving of life, not only of men but of the brutes as well, are demanding solution; the greatest hope for the solution of these problems lies in the continued use of animals for experimental purposes—so the situation presents itself to those engaged in the struggle with disease. Shall men suffer and die to save the lives of the experimental animals, or shall the experimental animals die to mitigate pain and wide calamity among men? That is the question.

The opponents of medical investigation speak for the animals, the investigators speak for man. Which lives are the more important? The question hardly needs answering. The mere thought of sacrificing human life for the life of a dog or cat is monstrous. It is a grotesque reversal of the world's values. To make such a sacrifice would be an act of insane folly. Yet in effect that is what the opponents of medical research really advocate.

The kindly motive of the antivivisectionists can not be questioned. Their intent is to diminish pain and suffering. They pity the dumb animals; to save the lives of these creatures they would check medical progress. The kindly motive is no doubt humane. But ignorance, and shortsightedness, and grotesquely distorted perspective render such humanity a real danger to human welfare.

THE NEED FOR EDUCATION.

In an earlier section of this paper I suggested that ignorance and misconceptions regarding the methods and the results of medical research were due, in part, to the failure of the profession to enlighten the public. The medical profession has, indeed, made very little effort to affect the public mind. This is not because people are not ready to be taught. A large part of

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every community is eager for education regarding the means of maintaining bodily health, the necessities and the methods of public hygiene, the history of the medical sciences, and the requirements for medical progress. The readiness of inquiring minds to consider these subjects is the basis on which the opponents of medical research are working.

Now the facts must be faced that we are living in a democracy, and that in a democracy the most potent force is public opinion. Public opinion is the result of education. At present the education regarding the use of animals for medical progress is almost entirely one-sided. The antivivisectionists are spreading broadcast in some communities hideous tales of cruelty, and are leading people to believe that these horrors are typical of what is daily occurring in laboratories. Pictures are published tending to harrow the heart of any one who has in him a love for animals. Meanwhile, nothing is being done to counteract the falsity of these impressions. That medical investigators are also men with tender sympathies and are sensitive to the infliction of pain, that they approach their work with reverence for the wonderful mysteries that every living body reveals, that with a keen sense of human suffering they are patiently searching for new truth in the spirit of far-seeing humanity—these facts are not made known.

The time is approaching, I believe, for this education to be started. The movement should not be confined to the medical profession, but should be taken up as a duty by every intelligent person who believes that any restraint on medical research is a danger to human welfare. Already, in England, a Research Defence Society has been started with Lord Cromer as its president. The purpose of the society is to make known the facts, the facts as to the use of animals in experiments, and the immense importance of these experiments to the well-being of mankind. These facts the society intends to diffuse among the people by published articles

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and leaflets, by lectures, and by answers to inquiries. Although the society has existed only a few months, it already has hundreds of members, from all departments of public life, representing every class of educated Englishmen and Englishwomen, and including many who have been actively engaged in preventing cruelty to animals.

Thus somewhat tardily in England, after research and teaching have been hampered by restrictive legislation for more than thirty years, it has seemed wise to appeal to the good sense of the people. In this country we have thus far refrained from open opposition to those who are hostile to animal experimentation. But a campaign of education will become imperative, if the attitude of the public continues to be shaped entirely by those who are opposed to medical research. The experience of England is before us. "In the mother-country our hands are tied by an act which was defined by one of the highest legal authorities as a 'penal' act; and though with us, as with others, difficulties may have awakened activity, our science suffers from the action of the state." These were the words of Sir Michael Foster at the Toronto meeting of the British Medical Association; and at the end of a review of biologic progress during the preceding thirteen years, he sounded this note of warning: "Some there are who would go still farther than the state has gone, though that is far, who would take from us even that which we have, and bid us make bricks wholly without straw. To go back is always a hard thing, and we, in England, can hardly look to any great betterment for at least many years to come. But unless what I have ventured to put before you to-day be a mocking phantasm, unworthy of this great association and this great occasion, England in this respect at least offers an example to be shunned alike by her offspring and her fellows."

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RESULTS OF OVARIAN TRANSPLANTATION ON BODY WEIGHT AND EGG WEIGHTS IN FOWLS.

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It seems that lack of growth follows the removal of and transplantation of ovaries in chickens. At the end of from six to twelve months the hens operated on are distinctly lighter than the controls. Also the eggs from the hens operated on weigh less than the eggs from the normal hens. As a rule, the weight of the egg and chick relative to the body weight is also less in the hens operated on.

During the second year both the actual weight of the egg and weight relative to the body weight in the hens operated on approach the normal.[1]

	1907-'08.	
Fowl.	Egg wt.	Body wt.
G 1 (control)	59.96	2020
G 2 (operated)	47.50	1790
G 3 "	43.44	1650
B M 1 (control)	57.50	2270
B M 2 (operated)	37.12	1770
B M 3 "	41.20	1540

	1906-'07.		1907-'08.	
Fowl.	Egg wt.	Body wt.	Egg wt.	Body wt.
B 1 (control)	60.1	1500	63.55	1350
B 2 (operated)	40.9	1250	51.17	1250
B 3 "	46.6	1250	.....	....
W 1 (control)	59.1	1480	59.01	1540
W 2 (operated)	49.2	1450	63.25	1750
W 3 "	48.6	1250	.....	....

1. For a fuller account of these experiments the reader is referred to an article by the author entitled "Results of Removal and Transplantation of Ovaries in Fowls," Journal of Experimental Zoology, July, 1908.

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EXPERIMENTS TOWARD A PHYSIOLOGICALLY ISOTONIC SOLUTION OF SALTS.*

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The solution that is almost always employed by surgeons and clinicians for irrigations and intravenous injections is the so-called normal saline solution. This is a solution of NaCl in water varying from 0.7-0.9 per cent, in strength and agreeing approximately with the tonicity of blood, that being the only property of blood which at the time that this solution was devised was sufficiently understood to be imitated. Since that time physiologists, for experimental purposes, have vastly improved this solution, taking into consideration the action of other inorganic salts, besides sodium chlorid. Nevertheless, these advances have not been utilized to any considerable extent in practical medicine. Originally this research had for its object the investigation of the possible advantages of using clinically a solution which conformed more closely to blood than the ordinary normal saline solution. Saline solutions, such as those of Ringer, Locke and others, which have replaced almost entirely the ordinary sodium chlorid solutions in laboratories of physiology, conform more nearly to the inorganic constitution of blood. However, little attention has been paid to other impor-

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tant properties of the blood which until recently have hardly been understood. Among these are:

1. The correct H and OH ion concentration.

2. The capacity for maintaining the proper reaction in spite of increase in acid or alkali.

3. The capacity for the transport of carbonic acid.

In view of this, I turned aside for the present from my original problem in order to attempt such improvements as seemed possible in the light of these recent findings. The present communication is confined to a report of the results of this undertaking.

The practical problem then, in a case like this, is to choose those characteristics of blood which are essential, ensure their proper establishment and to include as many of the other characteristics as may readily be obtained without sacrifice of simplicity of technic and permanency of the solution. The solutions most frequently employed, where a physiologically normal saline solution is required, are solutions of NaCl of such a strength as to be isotonic with the blood. The tonicity has always been considered the essential point. The experiments of Ringer, Locke, J. Loeb and others, have shown the importance of the addition of K and Ca to the saline solution, especially when this was to be employed to maintain rhythmical contractions in the isolated heart. Hédon and Fleig,[1] starting from the assumption that a physiologic solution should correspond as nearly as possible to the blood, prepared a solution which in addition to Na, K and Ca, contained Mg, and phosphoric and sulphuric acid. All these solutions possess also a varying degree of alkalinity due to the addition of $NaHCO_3$. The exact amount of each ingredient varies with the author and, in each case, has been determined empirically. With no other test than the physiologic it is apparent that considerable variations in constitution need not necessarily

1. Arch. Internat. de Physiol., 1905-1906, iii, 95.

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produce any marked effect experimentally. With the exception of the total concentration, the tonicity, which is more or less definitely fixed, the rules for making up a physiologic saline solution are therefore very indefinite.

However, facts in regard to the maintenance of the proper neutrality and the equilibrium between acids and bases in general, by means of which the CO_2 transport is effected in the animal organism, have recently appeared which, when applied to the preparation of a saline solution, not only give us more definite guides, but make possible the preparation of a solution more nearly like blood than any other so far devised.

The data at hand regarding the concentration of the inorganic constituents of human blood are necessarily very insufficient. The methods for obtaining reliable information require the use of large quantities of blood, and it is, therefore, not surprising that the majority of the determinations have been carried out on the blood of animals. Through the work of Bugarszky and Tangl,[2] Abderhalden[3] and others, we have a fairly complete knowledge of the inorganic constitution and concentration of the blood of a number of the domestic animals, including the horse, cow, sheep, goat, pig, dog, rabbit and cat. It has been found that, in its general characteristics, the blood of these animals shows a marked uniformity both as among the various species as well as between the animal blood and the human. Moreover, it is known that the constitution of the blood of the same species, and even of the same individual, is subject to variations at different times which approximate closely to the variations observed in the analyses of the serum of different species.

The constitution of the fluid portion of the blood has been obtained by calculation from quantitative determinations of the blood corpuscles and of the serum.

2. Arch. f. d. ges. Physiol., 1898, lxxii, 531.
3. Ztschr. f. physiol. Chem., 1898, xxv, 67.

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As, however, the methods available at present are not of such accuracy as to allow absolute dependence on figures obtained, it was considered wiser to simplify the procedure and to base the calculations for an artificial solution to resemble the body fluids on the figures for the serum, with the full realization that the result would be only a close approximation of the actual conditions. The human serum consists chiefly of water in which are dissolved about 8.5 per cent. solids. These consist mainly of albuminous substances and small quantities of sugar, cholesterin, lecithin and fat, and inorganic bases and acids. These latter are mainly Na, K, Ca, Mg, in combination with HCl, H_3PO_4, and H_2CO_3. By calculation based on the quantitative estimations of Abderhalden[4] of the inorganic content of blood serum the values shown in Table 1 were obtained in grams per liter:

TABLE 1.

Na_2O	4.45	Na	3.30
K_2O	0.26	K	0.21
CaO	0.12	Ca	0.08
MgO	0.045	Mg	0.03
Cl	4.0	Cl	4.0
P_2O_5	0.07	H_3PO_4	0.09

If these amounts are expressed as chlorids, phosphates and carbonates we obtain the results shown in Table 2:

TABLE 2.

KCl	0.40	K	0.21	Cl	0.19
$CaCl_2$	0.22	Ca	0.08	Cl	0.14
+6aq	0.4				
$MgCl_2$	0.12	Mg	0.03	Cl	0.09
+6aq	0.25				
NaCl	5.90	Na	2.32	Cl	3.58
				Cl =	4.00
NaH_2PO_4	0.11				
+1aq	0.126	Na	0.02	H_3PO_4	0.09
$NaHCO_3$	3.51	Na	0.96		
		Na =	3.30		

A solution containing per liter the amounts stated in Table 2 has precisely the same reaction as blood and possesses nearly the same power to neutralize both acids and alkalies, as shown by Henderson and Black.[5]

4. Abderhalden, E.: Ztschr. f. physiol. Chem., 1898, xxv, 67.
5. Am. Jour. Physiol., 1907, xviii, 250.

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The correctness of the reaction was further clearly shown when tested with rosolic acid paper, and agreed fully with the observation made by me on blood and reported in a previous communication.[6]

The monophosphates now constitute about 10 per cent. of the total phosphates, and free carbonic acid about 6 per cent of the total carbonic acid. In other respects the proper relationship between the several acids and bases is automatically adjusted by this method of preparation.

The inorganic constituents being thus properly adjusted, it remains to consider the organic. It is evident at once that the proteins of the blood can not very well be introduced into an artificial solution. However, one of the important effects of the presence of colloids in blood, the increase of the viscosity, can very well be brought about in an artificial medium by means of a colloid or colloids that do not coagulate with heat and that are more or less inert, or at least innocuous, in the animal organism. Two such substances are easily obtainable, viz: gelatin and gum arabic. Albanese[7] has shown that a 2 per cent. solution of gum arabic in water has a viscosity closely resembling that of blood, and his perfusion experiments convinced him of the importance of this factor. A considerable advantage of gum arabic over gelatin solutions is the fact that the former remains liquid at the temperatures required in the preparation of the fluid. The sugar content of the blood likewise was approximated by the introduction of 0.15 per cent. dextrose.

The effect of the addition of the colloid was remarkable in that it increased the solubility of the calcium salts and apparently held them in solution at a temperature and a CO_2 tension that, without the presence of colloid, caused a precipitate. The solution thus prepared had a freezing point of —.58 C, corresponding

6. The Journal A. M. A., 1907, xlix, 461.
7. Arch. f. exper. Path. u. Pharmakol., 1893, xxxii, p. 297.

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to that of human serum, and its osmotic pressure was further tested physiologically by using it to make a suspension of blood cells. The red cells retained their shape perfectly.

In Table 3 I have placed side by side the ordinarily used Locke's solution, the solution of Hédon and Fleig[8] and my own:

TABLE 3.

	Locke	Hédon and Fleig	Author
NaCl	0.9	0.6	0.59
KCl	0.025	0.03	0.04
$CaCl_2$	0.023	0.01	0.04
$MgSO_4$	....	0.03	$MgCl_2$ 0.025
NaH_2PO_4	....	0.05	0.0126
$NaHCO_3$	0.02	0.15	0.351
Glucose	0.10	0.10	0.15

It will be seen that in regard especially to NaCl, $NaHCO_3$ and NaH_2PO_4 these solutions differ considerably from one another. Locke's solution contains sufficient NaCl to produce an isotonic solution without any further additions. In other words, this solution must in most cases be slightly hypertonic. The omission of Mg and P_2O_5 from Locke's solution, while probably not important, certainly does to some extent affect the final equilibrium between acid and base. The $NaHCO_3$ is much too low to obtain the correct reaction. The same is true of the solution of Hédon and Fleig who on that account probably have kept the $CaCl_2$ so low. The solution suggested in this communication contains a comparatively large amount of $NaHCO_3$ and a small quantity of NaH_2PO_4 which together produce an equilibrium able to maintain the necessary amount of calcium in solution. If the $CaCl_2$ and the NaH_2PO_4 are separately dissolved and mixed with the other substances already in solution, no precipitate appears. If all the salts, however, are placed together in the necessary quantity of water a certain amount of calcium phosphate is formed. This precipitate will readily go into solution on passing CO_2 through the

8. Arch. Internat. de Physiol., iii, 95, 1905-1906.

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liquid. The reaction, however, will become more acid. After the salts are in solution, the excess of CO_2 can be driven off without causing a reappearance of the precipitate.

Aside from theoretical and practical chemical considerations, it seemed desirable to test the correctness of the solution as a physiologic fluid by experiments with the living organism. The molecular concentration of the fluid, as above stated, was made to approximate that of cat's serum by the addition of 0.15 per cent. NaCl. A number of experiments were conducted to determine how long an isolated cat's heart would beat rhythmically when perfused with this solution. The apparatus used was the one described by Cleghorn.[9] The cat's heart was removed as quickly as possible from the animal, and after it had freed itself of blood in a saline bath, was tied to a canula passed into the aorta just above the coronary orifices. The solution was then forced through the coronary arteries under a constant pressure of 60 mm. of mercury. The whole apparatus was kept at about 35 C.

The results obtained proved that this solution was well adapted to the requirements of a circulating fluid. In one case, under unusually favorable conditions, rhythmic contractions were maintained for 21 hours after the heart had been removed from the cat. No difference could be observed between the solution made up as above and one from which $MgCl_2$ had been omitted, and the NaCl content correspondingly increased. In regard to the viscosity, the solution containing 2 per cent. gum arabic gave rather less satisfactory results than the one without it. This could be explained possibly by the increase in K content of the solution, due to the gum arabic.[10]

It is worthy of note that the best results so far were obtained with those solutions which had no oxygen

9. Am. Jour. Physiol., 1899, ii, 275.
10. Locke: Jour. Physiol., 1895, xviii, 332.

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added. As the water was always freshly distilled, it is not likely that any large amount of oxygen was present, and it is conceivable that the CO_2 content of the solution acted as a stimulus. Furthermore, the solution is capable of holding and removing considerable quantities of CO_2, which, possibly, is quite as important as the presence of oxygen. Several experiments were tried in which the solution was saturated with oxygen and then perfused under oxygen at pressures of from 50 to 80 mm. of mercury. It could not be observed that this caused any more favorable result.

CONCLUSIONS.

While the experiments are as et incomplete it is, perhaps, not too early to say that the solution described above has certain qualities that recommend it for physiologic use. It approximates blood serum closely in its constitution, in the concentration of its various components and in reaction. It provides a mechanism, on the one hand, for maintaining the reaction, and, on the other hand, for neutralizing acids and alkalies. It provides for the transport of a sufficiently large amount of CO_2. The clinical application of this solution is still under investigation.

It is a pleasure to record my indebtedness to Dr. L. J. Henderson for help in the calculations, and to Dr. W. T. Porter for much valuable guidance as well as for generously placing their laboratory facilities at my disposal.

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THE BACTERIOLOGIC DIAGNOSIS OF TYPHOID FEVER.

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Since the introduction of modern laboratory aids in the recognition of typhoid fever the problem which has presented itself to practitioners of medicine is that of more accurate and earlier diagnosis. The demand for a scientifically accurate diagnosis is the outcome of the realization that clinical typhoid fever is a disease which may be caused by any one of several bacteria. The physician of the present day is no longer satisfied with the old term "enteric fever." He tries, so far as possible, to supplement his clinical diagnosis by an accurate bacteriologic diagnosis. The establishment of the bacteriologic diagnosis is only to be accomplished by the isolation of the specific organism infecting the individual patient.

From a practical standpoint the question of early diagnosis is of much greater importance than that of absolutely accurate diagnosis. To the individual patient early diagnosis in typhoid means better treatment, better nursing, perhaps more adequate domestic arrangements, and often a great saving of strength during the first stages of the disease. Moreover, if we are to have any specific method of treating typhoid, its value will probably depend to a great extent on the time at which its use is begun. In the sphere of preventive medicine the problem of the early diagnosis of typhoid has lately assumed enormous proportions. That the typhoid patient

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is a source of danger to the community during his sickness has long been recognized. That he may continue to disseminate the bacilli for months and years after his convalescence is now becoming a well-known fact. That he may, and doubtless often does, spread the contagion even before he shows any clinical symptoms of the disease, that the disease is infectious during the incubation period, has, however, only recently been proved. Conradi,[1] in a striking article, has demonstrated that the typhoid bacillus can be isolated from the blood of an apparently healthy individual, and has shown that in eighty-five cases of so-called "contact infection" the infection occurred in 58 per cent. of the cases during the first week. In the fight to limit the spread of typhoid fever the task of isolating and controlling the late dangerous cases, the chronic bacilli carriers, falls to a great extent on the public health authorities. The detection of the early bearers of contagion must, however, be the duty of the individual practitioner.

Although the bacillus of typhoid fever may be isolated from various sources, the only methods which have proved themselves to be of considerable value are the examinations of the urine, the stools and the blood. The first of these—the urine—has never come into special prominence as a routine procedure. The organisms can be isolated from the urine in about 25 per cent. of the cases, and often early in the disease; but this percentage of favorable results is hardly sufficient to warrant the method being used very extensively.

The examination of the stools as a diagnostic measure in typhoid appeared at one time to have a brilliant future. The conception of the disease as an intestinal infection went hand in hand with the idea that the dejecta swarmed with typhoid bacilli. The first difficulty encountered was the necessity of differentiating the typhoid from the colon bacillus. In answer to this need there was brought forward a long series of special

1. Deutsch. med. Wchnschr., 1907, p. 1684.

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culture media on which these organisms could be distinguished from one another with more or less accuracy. Some of these media were difficult to use, others comparatively simple. All of these methods, however, for their success depend on being used by skilled bacteriologists; and even so, the results obtained by them have not, on the whole, been favorable. In the hands of some observers they have done well, and there are many series of cases in which the bacilli have been isolated from a large percentage of the stools. Other equally good workers have failed to confirm these results and have only been able to find them in a comparatively small proportion of their cases. The conflicting reports as to the frequency of the presence of the bacilli in the feces are, however, at least partially explained in the light of our present knowledge of the disease. If, instead of regarding typhoid as a primary intestinal infection, we regard it as a primary septicemia, which usually has secondary intestinal lesions, with a secondary infection of the gall bladder, the uncertainty of finding the organisms in the stools is more easily accounted for. There is good reason to believe that the intestine and its contents form a very poor culture medium for the typhoid bacillus, for autopsy may show a gall bladder with bile so infected with typhoid bacilli that a single drop will give hundreds of colonies, while cultures from just below the ampulla of Vater, and from the intestinal contents at different points down to the cecum, will not show the presence of a single typhoid colony. It is possible, on the other hand, that the organisms growing in the gall bladder from time to time may be discharged into the intestine in such large numbers that many of them survive the passage of the intestine and may be isolated from the feces. It is a clinical fact that many negative examinations in a case may be followed finally by a positive examination, thus making the element of luck a prominent factor in the value of the process. The different results obtained by various observers may be ac-

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counted for also in some degree by the viability of the special race of organisms infecting the case. It is probable that some races of the typhoid bacillus are much more resistant to the hostile conditions in the intestine than are others. An analysis of the cases in which the organisms have been recovered from the stools shows that this method of diagnosis may often be useful in early as well as in late stages of the disease, but the difficulty of the technic, together with the relative uncertainty of the results, makes the method of comparatively small value as a routine procedure. The examination of the stools is, on the whole, chiefly important in the recognition of chronic bacilli carriers.

If typhoid fever is primarily a septicemia, it is natural to seek for the first signs of the disease in the blood itself. Since Castellani[2] first isolated the typhoid bacillus from the blood of a patient in 1899 the numbers of workers with blood cultural methods has shown a steady increase from year to year, and the literature on this branch of diagnosis has lately exceeded any other. Whereas the first reports on the subject were rather of bacteriologic and pathologic interest, the larger series of cases which have since been collected have shown that the method is of clinical value as well, and have begun to establish it on a practical basis.

The technic which has been most commonly used in making blood cultures has been thoroughly to clean the patient's arm and to take with a syringe about 10 c.c. of blood from one of the veins at the bend of the elbow. The blood is then distributed into several flasks of bouillon and diluted by the medium to such an extent that its bactericidal properties are overcome. Although this method has given excellent results in many hundreds of cases, there is no wonder that it has never become a routine procedure outside of a comparatively few large hospitals. It is distinctly a laboratory rather

2. Zentrlbl. f. Bakt., 1902, xxxi, p. 477.

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than a clinical method. Apart from the necessity of having a more or less trained bacteriologist to work out the culture, there are marked objections to the method itself. The culture medium is too bulky; it is often inconvenient to carry flasks of bouillon to the bedside. Then the technic of drawing the blood is not always simple. In fat persons, or in those with small vessels, it is at times almost impossible to insert the point of the needle into a vein. Of more importance, however, is the fact that to the patient and to the family the method must always appear to be a somewhat radical procedure. This is alone sufficient to limit the extent to which even a measure of recognized value will be used as a routine practice.

In order that any diagnostic method shall be accepted by practitioners in general, it must be stripped of all its technical difficulties and reduced to its simplest terms. Toward the accomplishment of this, and toward making the blood culture a practical aid in the diagnosis of typhoid fever, there has been much advance in the last few years. The first step of importance was the introduction by Conradi,[3] in 1906, of ox bile as a culture medium to replace bouillon. The peculiar advantage claimed for the new medium was that the bile salts prevent the coagulation of blood and the formation of bactericidal elements in the blood serum. Whether or not this explains the whole of the action of bile has been doubted. However, from the frequency with which the gall bladder is found infected at autopsy, and from the fact that in chronic bacilli carriers the gall bladder is the usual seat of infection, it is evident that bile must be especially well suited for the growth of the typhoid bacillus. By Conradi's original method, test tubes containing a mixture of ox bile with peptone and glycerin were used. The peptone was added to increase the growth and to aid in preventing coagulation of the blood. The glycerin was

3. Deutsch. med. Wchnschr., 1906, p. 58.

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to limit the growth of saprophytes. Kayser,[4] however, later demonstrated that as good results can be obtained from the use of pure ox bile alone, and he showed that if the blood added to the medium contains even as few as 2 or 4 bacilli the cultures after incubation will give a profuse growth. Working on another line toward a practical blood-cultural method, Müller and Gräf[5] have reported a series of cases in which they used small amounts of coagulated blood sent to the public laboratory for agglutination tests. After separating the clot from the serum, they used the latter for the agglutination, and the former they rubbed over the surface of Drigalski-Conradi plates. The plates were then incubated, and in 360 cases, including convalescents and chronic bacilli carriers, they were able to isolate the organism in 110, including 10 cases of infection with the paratyphoid bacillus. The disadvantage of such a plate method is that there is no increase in the number of organisms, and if not numerous they might be overlooked or overgrown by saprophytes. Fornet[6] has devised a method analogous to that of Kayser, in which he also uses the clot of blood sent in to be tested for the agglutination reaction, planting it in bile, and examining the culture after incubation. Of a series of 19 cases, 14 gave positive results. It is not expected that this will replace the technic of Conradi and Kayser, but it is a valuable method when it is impossible to get the uncoagulated blood into bile.

Of these various simplified blood cultural methods, one of the most satisfactory is the use of the medium of Kayser with small amounts of blood obtained from the patient's ear.[7] The technic is as follows: The lobe of the ear, after being carefully cleansed with sterile gauze and alcohol, is pricked rather deeply with a small lancet-pointed knife, the blood squeezed out drop

4. Kayser: Münch. med. Wchnschr., 1906, pp. 823 and 1953.
5. Zentrlbl. f. Bakt., 1907, xliii, p. 856.
6. Münch. med. Wchnschr., 1906, p. 1053.
7. Peabody: Arch. Int. Med., 1908, i, p. 149.

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by drop, and allowed to run into a test tube containing about 5 c.c. of plain, sterile ox-bile. It is usually easy to collect 2 c.c. of blood without any inconvenience to the patient. The mixture of blood and bile is then placed in the incubator at 37° C. for from 12 to 15 hours, after which a few loopfuls are transferred to a tube of Löffler's blood serum. In some cases, examination of a drop of the original bile culture after incubation shows the presence of a motile bacillus, but more often this is better demonstrated in the water of condensation of the blood-serum tube after about five hours. The presence of a motile bacillus is in itself excellent evidence in favor of an infection by one of the typhoid group; but in order to prove the organisms it is customary to test them for their cultural characteristics and for the agglutination reaction.

That this simplified method is one of clinical value has been proved many times. At the Massachusetts General Hospital, where it has been used as a routine measure in all cases of typhoid during the past few months, it has been the means of establishing the diagnosis in 55 of 82 cases examined. In 28 per cent. of the cases the culture gave the diagnosis before the agglutination test. In the first week the culture was positive in all of 17 cases; in the second week, in 70.2 per cent. of 37 cases, and in the third and fourth weeks, in 42.8 per cent. of 28 cases. The agglutination test was positive in 52.9 per cent. of the cases in the first week, in 67.5 per cent. in the second week, and in 82.1 per cent. in the third and fourth weeks. The results are similar to those obtained in larger series of cases, in which the old method of taking a greater amount of blood from a vein has been used.

It is thus evident that in the ox-bile culture method we have a measure of considerable diagnostic importance in the early stages of typhoid fever. It is, moreover, a method which can be used, not only by trained bacteriologists, but by any practitioner. When a man

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can not do his own bacteriologic work the culture may be sent to a laboratory to be worked out. In Germany some of the large chemical firms have put on sale tubes of bile so sealed that they can be sent through the mail to the public laboratories, where the cultures are incubated and the diagnosis made in the same way in which the public health laboratories in this country perform the agglutination reaction. The physician merely has to prick the patient's ear, collect the blood, and put the tube in the mail. The technic is thus only slightly more troublesome than that of the Widal reaction, and when it is considered how valuable the method is in making an early and accurate diagnosis it would seem that the blood culture must assume a major rôle in the future.

Of all laboratory methods in the diagnosis of typhoid fever there is none which has been used so extensively, or has given such excellent results in the hands of many clinical observers, as has the agglutination reaction. That it has been generally adopted the world over is due to its high degree of accuracy combined with its simplicity. The establishment of public laboratories, where samples of blood are examined for individual practitioners, has brought the test within the reach of a vast number of physicians. While, however, the reaction has proved itself of inestimable value, there are certain important drawbacks to its use. The chief of these is that the agglutination reaction is often late in making its appearance. It is frequently not obtained during the first week of the disease, and while it is present in about three-quarters of the cases during the second week, it may be delayed much longer, and even into convalescence. Its value is, therefore, limited at the very period in the disease in which a diagnostic test is most needed; for while it is often comparatively simple to recognize typhoid fever in its later stages, it is at the onset, during the first week, that the most doubt arises, and it is in the early days of the disease

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that the danger of contact infection is probably greatest. Moreover, there are certain atypical cases in which the reaction is never obtained. Next to the lateness of the appearance of the agglutination test, its greatest disadvantage is that it is not absolutely specific. It does not always give an etiologic diagnosis. That an agglutination of the typhoid bacillus may be produced by the serum of a patient infected with one of the paratyphoid bacilli is not of great clinical importance; but that the test may be obtained in cases in which the etiologic organism is the pneumococcus,[7] the *Bacillus proteus*,[8] or some other organism not closely allied to the typhoid group, is a fact not to be neglected. The exact percentage of error in the agglutination test it is, of course, impossible to calculate. That it is, however, a very appreciable error any one who has had occasion to use the test extensively must realize. In spite of the fact that the agglutination reaction is in itself by no means an ideal diagnostic measure, it is of the utmost value in certain cases, and especially so when taken in conjunction with the blood culture. In the early stages of the disease, before the agglutination test is positive, the diagnosis is made in most cases by the culture; and in the later stages, when the organism can no longer be isolated from the blood, the agglutination reaction is usually present. Thus the one test is supplemented by the other, and in these two comparatively simple clinical methods—the agglutination test and the blood culture in ox bile—we have the means of making an accurate diagnosis of typhoid fever, in the great majority of cases, at any stage in the course of the disease.

DISCUSSION.

Dr. R. L. Jones, Nashville, Tenn.: One of the most important additions to our knowledge of the subject of typhoid fever made in recent years is the means for an early diagnosis, which has been made practicable for us by Dr. Peabody. He will place us under still further obligation if he will make the

8. Zeit. f. klin. Medizin, 1905, p. 27.

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technic clearer. I have been engaged in this work and have had to work out some of the technic myself. Does the kind of ox bile used make any difference? I find that it is quite different when you get a steer in good condition whose bladder contains considerable bile; the bile will be of a bright green color, while that from a cow or steer not in good condition is more apt to be of a golden yellow color. Butchers tell me that this is the rule. This bright green bile if kept some time will change to the golden yellow color, and I have found that it takes the typhoid organisms longer to develop in the golden yellow bile. If Dr. Peabody uses fresh bile I would like to know how fresh; how long it will keep after sterilizing; and if there is any method by which we can keep it indefinitely in stock.

DR. FRANCIS W. PEABODY, Boston: I can only say that we have never had any trouble at all. We have taken the bile from several different animals and used it as it came from the slaughter-house. Lately we have been using pig's bile, which seems to give as good results. As to keeping the bile after it is sterilized, we have had no difficulty on this point, and have used successfully bile that was four months old. It was sterilized as soon as it came from the slaughter house, kept in bulk in the ice chest, and put into test-tubes as it was needed.

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TYPHOID BACILLI CARRIERS.

WILLIAM H. PARK, M.D.
NEW YORK CITY.

The obscurity of the origin of a large percentage of typhoid fever outbreaks led many observers to the supposition that perhaps some saprophytic member of the colon group might change under bad hygienic conditions to the typhoid bacillus.

Further investigation revealed the fact that a small percentage of persons after recovering from typhoid fever pass typhoid bacilli in the urine. The attack of typhoid fever in some of these cases had been a number of years before. Continued examinations showed that these cases were comparatively rare, and it did not seem possible that they could account for all outbreaks of typhoid fever, where one could not trace the infection to those having the disease.

In 1902 von Drigalski and Conradi found typhoid bacilli in stools of four persons who had had no typhoid fever symptoms, but had been in contact with typhoid patients. Soon it was found that a number of typhoid convalescents continued to pass typhoid bacilli for long periods after recovery. Examinations of persons who had had typhoid fever years before revealed the remarkable fact that 1 or 2 per cent. of them were passing typhoid bacilli, sometimes in enormous numbers. The knowledge that the gall bladder had been found infected at operations for calculi suggested this as the source of the bacilli.

A number of autopsies or operations have since been held on these typhoid bacilli carriers and proven this to

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be the case. Thus, Levi and Kayser reported, in 1906, a case of a woman, 49 years old, who had had typhoid fever in 1903 and made a good recovery. In 1906 the woman died from some other disease; autopsy was held nineteen hours after death. Typhoid bacilli were present in the liver, in the wall of the gall bladder and inside a number of calculi.

Kayser reports that in Strassburg during the year 1904-5 13.5 per cent. of all cases of typhoid were traced to 6 of these typhoid carriers, all of whom were women and gave histories of having had typhoid from one to 27 years before.

A large number of cases of typhoid fever have now been traced to these chronic bacilli carriers. Thus, Lentz states, in 1905, that seven physicians had then reported typhoid cases from bacilli carriers. The first reports the case of a patient who had had typhoid 3 years before, who was known to cause 2 cases of typhoid; the second reports 4 typhoid carriers, who had had typhoid as long ago as 42 years, 15 years, 13 years and 12 years, respectively. To these 4 were traced 12 cases of typhoid. The third reports a typhoid carrier who had typhoid 19 years before, who caused 6 cases of typhoid. The fourth reports a carrier who had had typhoid 1½ years before, but to whom no cases had been traced; the fifth had a patient who had had typhoid 17 years before and had caused 27 cases; the sixth had a patient who had had typhoid 10 years before and had caused one other case, and the seventh reported a bacilli carrier who had had the disease 17 years before. To this last individual 2 cases were due.

Out of 400 recorded typhoid patients Lentz found that 6 retained the bacilli at the end of periods ranging from 3⅓ to 13 months. Klinger examined the feces of 1,700 healthy persons who had never knowingly had typhoid and found bacilli in 11.

When the bacilli were in the stools of typhoid carriers, Lentz found that he could not get rid of them by

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any treatment. Their retention is due, he thinks, to faulty metabolism and concomitant chronic disease. Faulty care during convalescence may also be a cause.

He notes the predominance of women who are carriers over men, and especially married women who have borne children.

In most cases, the bacilli are present in great numbers. Lentz suggests that the gall bladder may not be the only source, but that the appendix and the deeper folds of the intestine may also be involved.

In conclusion, he suggests the following procedures for controlling these carriers. These, as we note later, can hardly be carried out except in special cases.

1. Disinfection of stools.
2. Disinfection of privies.
3. Police notification.
4. Bacteriologic control of stools.
5. Prevention of any occupation in which the carrier is in a position to infect others.

INVESTIGATIONS ON TYPHOID CARRIERS AT THE RESEARCH LABORATORY DEPARTMENT OF HEALTH.

History.—On March 20, 1907, a cook was brought to the laboratory to have the feces and urine examined. The history as developed by Soper revealed the fact that during the past eight years she had been employed in eight families and in seven of these typhoid fever had broken out within a few weeks or months of her arrival. In all twenty-six cases and one death occurred. Just before her removal to the Department of Health two cases had developed in the family where she resided and one patient died. Bacteriologic examination revealed the fact that fully 30 per cent. of all the bacteria voided with the feces were typhoid bacilli. The urine was negative. Careful cultural and agglutination tests showed that they differed in no respect from bacilli obtained from acute cases. The repeated outbreaks occurring after her entrance in families were in themselves proof that the virulence of the bacilli had remained intact. A curious feature of the case is that the woman denies that she ever had typhoid fever.

Treatment.—This woman has now been isolated for sixteen months. Weekly examinations of the stools have usually

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revealed large numbers of bacilli, but there have been several intervals when for one or two weeks no bacilli could be detected. Treatment by intestinal antiseptics has proved unavailing. Hexamethylenamin in doses gradually increasing from 100 up to 150 grains a day, has been given for a number of weeks with no apparent benefit. Attention to diet and mild laxatives has caused the greatest reduction, but not their disappearance. This suggests that the chief development of the bacilli is in the intestines, although the source of the infection is probably the gall bladder.

The case of this woman brings up many interesting problems. Has the city a right to deprive her of her liberty for perhaps her whole life? The alternative is to turn loose on the public a woman who is known to have infected at least twenty-eight persons.

This case excited so much interest that I decided to have tested a large number of typhoid convalescents. Eight months ago there was a typhoid epidemic at the Trenton (N. J.) State Insane Asylum. Through the courtesy of those in charge we were able during the past two months to examine the stools from 52 persons who had had typhoid at that time; 2 of these were found to pass numerous typical typhoid bacilli. Their stools were examined four times. One case revealed the bacilli only once, in the other they were present every time.

The stools of 16 persons, who had suffered from typhoid fever in the Long Island State Asylum, were sent us by Dr. Agnew. Two of these persons were found to pass abundant typical typhoid bacilli; they had been well for six months. Repeated examinations have shown the constant presence of bacilli. One of these cases was so mild that the patient was only suspected to have typhoid fever because of the other cases of that disease.

We have, therefore, found typhoid bacilli in the stools of 6 per cent. of the cases examined. During the autumn we examined the feces from a large number of persons convalescent from typhoid fever just as they

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left the hospital and found bacilli persisted in the feces of about 5 per cent. It was impossible to trace the cases further.

The bacteriologic tests were carried out by Dr. Goodwin and the Misses Noble and Pratt, bacteriologists in the Research Laboratory.

These examinations indicate that the same conditions exist in this country as in Europe, namely, that fully 2 per cent. of persons who have had typhoid fever are typhoid bacilli carriers. A few of these pass infected urine, but most infected feces. Besides these there are numerous typhoid carriers who never had typhoid fever, but through contact with infection became bacilli carriers. Probably at least one in every five hundred adults who have never knowingly had typhoid fever is a typhoid bacilli carrier.

As the majority of typhoid cases occur before the age of 30, the average life of typhoid carriers is fully 25 years, so that we have the somewhat appalling fact that there are at least half as many recovered typhoid cases who are typhoid carriers as there are typhoid cases in any year and that, besides these, there are the typhoid carriers, such as the cook, who have never had typhoid fever.

What can we do under these circumstances? It seems to me that any attempt to isolate and treat on bacteriologic examinations, as Lentz suggests, is impracticable. When we consider that the presence of the bacilli in the feces of these persons is often only occasional, that numerous contact cases having never had typhoid fever would not come under suspicion, and finally, the impracticability of isolating for life so many persons, we are forced to consider isolation utterly impracticable, except as in the case of the cook already described, where conditions increase the danger to such a point that an attempt at some direct prevention becomes an essential.

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We must, therefore, as before, turn to the more general methods of preventing infection, such as safeguarding our food and water, not only chiefly when typhoid fever is present, but at all times, for we now know that in every community, whether it be large or small, unsuspected typhoid bacilli carriers may always be present.

DISCUSSION.

DR. HENRY ALBERT, Iowa City, Iowa: A small epidemic of typhoid fever, traceable to a bacillus carrier, occurred in Cedar Falls, Iowa, last fall. It was an epidemic of thirteen cases of typhoid, occurring at about the same time in three families that lived in the same neighborhood. The water supply was first investigated and it was found that these families were using the ordinary supply of the city, the same as that used by a majority of the people. The water supply as the medium of infection having been ruled out, the milk supply was next investigated and it was found that the families in which the cases of typhoid occurred all obtained their milk from one source, and that no other family in the city was supplied from this source. We then investigated more in detail as to the possibility of the contamination of the milk and found that the owner of the cow, who also did the milking, had had typhoid about fifteen months previously, but had not had a sign or symptom of typhoid since, or for more than a year. A bacteriologic examination of the urine and feces of this man was made and typhoid bacilli found in the urine in considerable number. There was no evidence of an inflammatory condition of the kidneys or bladder. We felt reasonably certain that the epidemic was caused by this bacillus carrier. Hexamethylenamin in the form of urotropin was given and in a few weeks the urine was free from the typhoid bacilli. I feel certain that other epidemics I have observed in the past were caused by individuals of this kind.

DR. WILLIAM LITTERER, Nashville, Tenn.: The subject of typhoid carriers is an exceedingly important one. I have in mind a patient who had typhoid fever one year ago. The patient subsequently developed a post-typhoid necrosis of the rib which was operated on by Dr. W. A. Bryan of Nashville. A sinus appeared and a large amount of pus exuded from this wound, something like four or five ounces a day. This condition existed for three months, the patient growing weaker, rapidly losing flesh, and vague pains developed throughout the body. The surgeon requested that I isolate the organisms in said pus and make a vaccine according to the method of Wright. This I did and much to my surprise I found pure culture of the *Bacillus typhosus* in enormous numbers. I take this to be unique inasmuch as no other organism, such as the

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pyogenic cocci or other bacteria could be found in this exuding sinus of over three months' standing. I made a comparative estimate of the number of typhoid bacilli in this pus and found that an ordinary platinum loop full contained nearly a half million of bacilli. This case could be rightfully considered as one of a typical typhoid carrier and an especially dangerous one if the discharges from the sinus were not destroyed. Two months' injection with the autogenous typhoid vaccine produced very gratifying results. The patient is much stronger, gaining steadily in weight and there is an absence of the vague pains throughout body. The sinus has almost healed, only about half a dram of pus exuding in the twenty-four hours. Recently I made another bacteriologic examination and found only a few typhoid bacilli and some specimens of *Staphylococcus pyogenes aureus*. If the patient ceases to improve I intend to make a staphylococcic vaccine and inject this, with the typhoid vaccine. Dr. Park has called attention to the fact that many of these "carriers" have an infected gall bladder, and it has been suggested by some that, in order to cure this condition, a surgical operation would be necessary. It might be possible to try vaccine therapy in curing these conditions.

DR. M. J. ROSENAU, Washington, D. C.: I can not take Dr. Park's place, but feel sure that if he were here he would say that "typhoid Mary" refuses to submit to surgical interference. She is perhaps justified in this conclusion, because the gall bladder is not the only source of the typhoid bacilli that appear in the feces. Surgical interference therefore may not always correct the condition. Sometimes the feces of these carriers contain such large numbers of typhoid bacilli as almost to displace the colon bacillus; it seems that the typhoid bacillus may take up a natural habitat somewhere in the intestinal tract indepedendent of the gall bladder. We have not been able to find a chronic bacillus carrier of this type in Washington.

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METABOLISM IN TYPHOID FEVER.

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NEW YORK.

I shall not attempt to review the many-sided subject of metabolism in typhoid fever, but shall devote the time to a brief discussion of one phase of the subject, which is of great importance, as well as of interest, both to the clinician and to the pathologic physiologist.

During the course of the disease a typhoid patient loses from ten to sixty pounds, or even more, of his body tissue. This loss is divided among water, subcutaneous fat and protein from the body fluids or cells. The loss of water we may leave out of consideration because we know neither its amount or significance. Since the observation of Leyden[1] in 1869 it has been believed that there is a retention rather than a loss of water from the body in fever. This belief is supported by the decreased quantity of urine and by the supposed decrease in the evaporation from the skin; but few or no accurate data on this question are available, and no positive statements concerning it can be made.

The burning of body fat may, in the absence of carbohydrates, and perhaps also other conditions, lead to varying degrees of acidosis, with an abstraction of alkalis from the tissues, and possibly in other ways may be of distinct harm to the patient. This is borne out by the clinical observation that fat individuals are comparatively poor subjects for typhoid fever, or for

1. Arch. f. klin. Med., 1869, v, 366.

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that matter, for any infectious fever or for surgical operations. We have, however, as yet no good reason for believing that the metabolism of fat in fever is in any way different qualitatively from that in other conditions of undernutrition; and it seems to me probable that the excretion of the acetone bodies occasionally recorded in typhoid fever is merely the result of a burning of body fat in the absence of sufficient carbohydrates—the frequently observed starvation acidosis. If this is true, acetone, diacetic and beta-oxybutyric acids will not be excreted by the typhoid patient who receives an abundance of carbohydrates. Aside from the production of organic acids in the burning of body fats, the mere loss of fat is probably of no great consequence.

In addition to the loss of body fat there is a great loss of body protein in typhoid fever, and this is what I shall speak of in some detail. Many data are to be found in the literature as examples of the amount of this loss of protein. In a case reported by Leyden and Klemperer[2] there was a loss of 109 gm. of nitrogen, the equivalent of 3.2 kilos or seven pounds of pure muscle tissue in twelve days. In a case of Frederick Müller[3] there was a loss of 86.4 gm. of nitrogen, the equivalent of 2.5 kilos or five and one-half pounds of muscle tissue in eight days. These are not very unusual figures; a loss of the equivalent of even one and one-half pounds of muscle tissue in a single day is not very rare. There are many reasons for believing that this febrile loss of protein from the body is a serious and dangerous proceeding. The emaciation, muscular weakness and decreased resistance, and the long convalescence are certainly in part the results of the loss of body protein. The amount of protein lost appears to bear a close relation to the severity of the disease, and Ewing believes that the pathologic processes concerned in the metabol-

2. Von Leyden: Handbuch der Ernährungstherapie, 1904, ii.
3. Cong. f. inn. Med., 1902, p. 192.

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ism of this body protein take a prominent part in determining the patient's condition. Ewing's[4] idea is that many of the phenomena of typhoid fever, especially in the severe and fatal cases, are due to an autointoxication resulting from the "burning of thirty pounds of body tissue in three weeks"—and not directly to the endotoxins of typhoid bacilli. This idea is to some extent supported by the fact that the so-called nitrogen partition of the urine in severe or fatal cases is decidedly abnormal, and similar to those found by Wolf, Ewing and others in toxemia of pregnancy. Furthermore there are severe so-called toxic cases of typhoid fever which terminate with acute yellow atrophy of the liver, a condition which appears to be closely associated with a particular type of faulty protein metabolism. But aside from the possibility of its creating an autointoxication, the consumption and loss of body protein must be of great harm to the patient, both during the disease and during convalescence.

The causes for this loss of body protein are apparently three in number.

The first is partial starvation. An individual is obviously undernourished unless he absorbs from the digestive tract food of sufficient caloric value to equal the energy expended. Except by very difficult and accurate measurements it is impossible to know the amount of energy being expended by a particular patient, and few such measurements have been made on fever patients; but we may readily calculate average figures which are satisfactory for practical purposes.

At ordinary rest the heat and other energy expended by a normal individual receiving sufficient food is about thirty-three calories per kilo body weight. In fever there is an increased heat production, with an average, according to Krehl, of 20 to 30 per cent. Twenty-five

4. Proc. Path. Soc. Philadelphia, 1905; paper before New York Acad. Med., New York Med. Rec., 1907, p. 537.

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per cent. added to the thirty-three calories gives about forty calories, or, for a patient weighing seventy kilograms, or 150 pounds, 2,800 calories. This represents the minimum amount of energy which the average typhoid patient is expending in each twenty-four hours. If he does not receive food equivalent to this amount of energy he merely draws on his body tissues to make up for the deficit. Few or no typhoid patients receive enough food to maintain an equilibrium, and they consequently burn up for fuel varying amounts of their body fat and protein.

Any physician can readily calculate the probable deficit with the diets he uses. The deficit in calories is usually about 50 per cent., and this, according to von Noorden's figures,[5] may be responsible for loss of 2 to 3 gm. of body nitrogen per day.

The two other causes for the febrile loss of body protein are the pyrexia and the action of the bacterial toxins. From the experiments of Linser and Schmidt,[6] Fritz Voit[7] and Schleich,[8] we know that artificially raising the body temperature causes an increase in protein metabolism. The pyrexia itself is therefore one of the causes for the loss of body protein; but the loss due to this cause can be prevented, just as the loss due to partial starvation, by the intake of sufficient food.

The third factor is the so-called "toxic" destruction of body protein from the poisonous action of the bacterial toxins on the body protein. This last factor is still open to discussion, but I am inclined to the belief that some such action does take part. It is, however, at present impossible to discuss the toxic destruction apart from the result of the pyrexia, because we can not distinguish between the two when both are present, as they usually are in typhoid. The question which is of im-

5. Handbuch der Pathologie des Stoffwechsels, 1906, i, 497.
6. Arch. f. klin. Med., lxxix, 514.
7. Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in München, 1895, No. 2.
8. Arch. f. exp. Pathol. u. Pharmakol., iv, 82.

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portance for the practical treatment of typhoid is, can the combined effect of the pyrexia and the bacterial toxins be prevented from causing a loss of body-protein? There are already some encouraging answers to this question. May,[9] working with rabbits infected with pig erysipelas, was able to decrease the febrile loss of body protein by carbohydrates; though May later doubted the correctness of his first interpretation. Puritz[10] worked on human typhoid in St. Petersburg, and his results led him to favor a liberal diet in this disease. His diets, however, were rich in protein and of only moderate caloric value, and were therefore, I believe, not well adapted for his purpose, which was to retard the loss of protein. Weber,[11] working with a sheep inoculated with an extract of glanders bacilli, was able wholly to prevent any febrile loss of body protein by giving the animal a liberal diet containing much carbohydrate. Leyden and Klemperer, on the other hand, conclude from their experiments on typhoid and pneumonia that, while a liberal diet is desirable, it is not possible to prevent the febrile loss of protein; this view is generally accepted.

Last summer Dr. Warren Coleman and I undertook in Bellevue Hospital, New York, a further study of the extent to which the loss of body protein in typhoid fever might be retarded by dietetic means.[12] Our results were on the whole very encouraging, in that we were able to diminish the loss of body nitrogen to a comparatively small amount during the fastigial temperature and were able to make patients gain body protein during the steep curve period of the disease.

I need not here go fully into the reasons underlying our choice of diet, which is the opposite of that used by Puritz, and indeed the opposite, in some particulars, of

9. Ztschr. f. Biol., 1894, xxx, 1.
10. Virchows Arch. f. Path. Anat., 1893. cxxxi, 327.
11. Arch. f. exper. Path., xlvii, 10.
12. We are indebted to Dr. Armstrong, medical superintendent of Bellevue Hospital, for placing the facilities of the hospital at our disposal. The experiments will be published elsewhere in detail.

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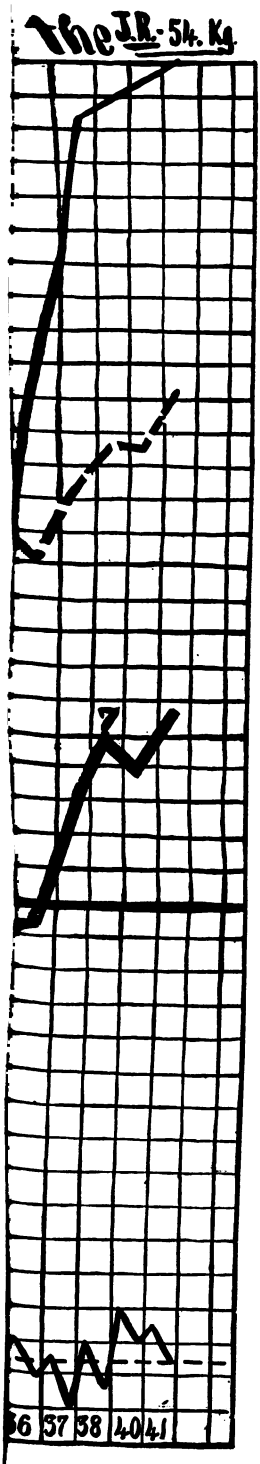

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the diets at present used in typhoid fever by most physicians. Our principle has been to have the diet contain a moderate amount of protein and the largest possible amount of carbohydrate. The reasons for choosing carbohydrates as the basis of the diets were briefly as follows: Carbohydrates are the strongest sparers of body protein in health, according to Voit, Lusk, Folin and others; and the experiments of May, Weber and Linser and Schmidt indicate that this sparing action takes place in fever as it does in health.

TABLE OF COMPOSITION OF FOOD DURING EXPERIMENT SHOWN IN CHART.

The numbers at the left refer to corresponding numbers on the "nitrogen balance" curve in chart.

		Gm.	Calories.	Per Cent. Total Calories.	Calories Per Kg. Body Wt.
1.	Protein	60	245	7.8	
	Fat	80	745	23.7	
	Carbohydrate	525	2150	68.5	
			3140		58.
2.	Protein	56	230	6.2	
	Fat	78	725	19.5	
	Carbohydrate	670	2750	74.3	
			3705		69.
3.	Protein	53	217	8.7	
	Fat	63	585	23.6	
	Carbohydrate	410	1680	67.7	
			2482		46.
4.	Protein	75.5	310	8.2	
	Fat	120.4	1120	29.8	
	Carbohydrate	569	2330	62.0	
			3760		70.
5.	Protein	16.2	66	2.0	
	Fat	108	1004	30.3	
	Carbohydrate	547	2240	67.7	
			3310		62.
6.	Protein	84	345	20.0	
	Fat	96	893	51.7	
	Carbohydrate	120	490	28.3	
			1728		32.
7.	Protein	85	349	8.8	
	Fat	122	1234	28.7	
	Carbohydrate	583	2390	62.5	
	Alcohol		80		
			3953		73.

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A large amount of fat is objectionable because of its tendency toward digestive disturbances and diarrhea; and the protein should be kept at the minimum effective amount because of its action in increasing the heat production (Rubner) and because of the large amount of work it throws on the intestine and the kidneys. The results from one of our cases are given in the accompanying chart. Samples of the diets used are given in the table.

Our results with other cases show essentially the same thing, although in some cases there was no gain, but a continued slight loss of one gram or so per day. On the high caloric diets, however, the patients were almost always in a condition not far from nitrogen equilibrium.

Our results show, we believe, that the febrile loss of body protein, including the result of the three factors, undernutrition, pyrexia and the action of toxins, may be retarded and even wholly prevented, or compensated for. But the results show likewise how difficult this is to accomplish. It was only when we gave sixty to seventy or even eighty calories per kilogram—between 3,000 and 4,000 calories—that the greatest sparing was observed.

The important point is, however, that it is possible to give typhoid patients such liberal diets without, so far as our experience shows, producing any harmful results, but, we believe, with decided benefit.

Having learned that it is possible to retard the febrile loss of body protein, we have still to decide whether it is desirable to do so in typhoid fever.

There are many objections, some apparent and others real, and many formidable difficulties; but I know of no reason why we should not attempt to do all in this direction that the circumstances will allow. Among the possible objections to liberal feeding in typhoid is the commonly supposed digestive limitation of these patients. The digestion in typhoid fever undoubtedly has

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its limitations, but they are not such as to prevent the proper absorbtion of amply sufficient food if given in the proper form. The experiments of von Hoesslin,[13] Leyden and Klemperer,[12] Puritz,[10] Folin[14] and others show very positively that the average typhoid patient absorbs food from his intestine almost as completely as does the healthy individual. Only in the severest cases is the absorption very materially decreased. In the average case without profuse diarrhea the digestion of protein, fat and carbohydrate is within 10 or 15 per cent. of the normal. Folin,[14] in his recent work on typhoid, has directly determined the degree of absorption of carbohydrates and has found it practically normal.

What seems to me an objection to liberal feeding in typhoid fever is the effect of the protein in increasing the heat production. Rubner[15] has shown how a strict protein diet in a dog may increase the heat production more than 50 per cent. The effect in a human patient could never be so great, but with the decreased heat loss in fever it is quite possible that this factor may be of considerable importance. This objection does not hold against the diets Coleman and I have used, but may apply to the high protein diets used by others. Carbohydrates have only a very slight effect in increasing heat production.

The objection has been raised to the use of large quantities of carbohydrates, from the fear of fermentation and tympanites. I can only say that we have had no such experiences with the use of milk sugar or starch.

The greatest practical difficulty that we have so far encountered in this work is the choice of food products. After trying or considering various carbohydrates we have used milk sugar almost wholly. This has the advantage of fermenting only with difficulty and of be-

13. Virchows Arch. f. Path. Anat., 1882, lxxxix, 317.
14. Unpublished experiments.
15. Rubner: Die Gesetze des Energieverbrauchs, 1902.

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ing less sweet than cane sugar and much more soluble than any form of starch. Milk, diluted cream, and eggs have been used to furnish protein and fat. Cocoa, lemon juice, tea, coffee and other things have been used as flavoring agents and as vehicles for milk sugar.

The patients did not object to our diets more than to milk alone, but some persuasion was frequently necessary to get them to take the amounts of food found to be necessary for our purposes.

The full advantages as well as the possible objections to our dietetic plan have still to be demonstrated; but there are a few reasons in favor of such liberal nourishment for typhoid patients which are worthy of consideration at this time.

As I pointed out earlier, the average typhoid patient receives at present 50 per cent. or less of his energy requirement. This is half starvation; and we know that starvation is harmful even in health, in that it leads to weakness and to an increased susceptibility to many infectious diseases. If starvation is harmful in health why should it be beneficial in typhoid fever? During the course of typhoid fever great demands are constantly being made on the defensive power of the organism; and it certainly does not seem probable that the patient will be as well prepared to meet those demands when in a starved or half-starved conditions as when he is being supplied with sufficient energy in the form of food.

It is a common laboratory observation that strong, robust, well-fed animals develop the strongest artificial immunity; and it seems fair to believe that we are assisting the patient to acquire his immunity to typhoid fever by keeping his nutrition at the highest possible level. Is it not possible that one of the factors determining the outcome of the disease may be the state of nutrition in which the body cells are maintained? Retarding the loss of body protein should leave the patient at the end of the fever in better physical condition and so make possible a shorter convalescence.

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This sort of reasoning is, however, largely speculative; and long experience alone can tell the true value of such treatment. We can merely say at present that it is possible by the means already outlined to retard and even to prevent the febrile loss of body protein.

414 East Twenty-sixth Street.

DISCUSSION.

DR. LAWRENCE LITCHFIELD, Pittsburg: During last summer I spent a great deal of time reading all I could find in the Surgeon General's Library on metabolism in typhoid, and from the crude experiments of Leyden, published in 1869, attempts made by increased feeding to prevent or control the loss of weight during the course of the fever, through the work of von Hösslin, whose classic article was published in 1882, and the excellent work of von Leyden, Klemperer and others down to that of Lüthje, who published in 1902 the report of his successful attempts to establish a plus nitrogen balance during the period of steep curve, though with very high proteid feeding, this work of Drs. Shaffer and Coleman is unquestionably the best that has been done on the metabolism of typhoid up to the present time.

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THE TREATMENT OF TYPHOID FEVER.

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BALTIMORE.

There is no intention in this paper to endeavor to discuss all the phases of the treatment of typhoid fever, but those will be considered about which there is the greatest difference of opinion or which deserve special emphasis. In the consideration of the handling of a patient with typhoid fever we must always have the individual in mind and care for him rather than treat a disease. No one method suits every patient any more than clothing made to one measurement fits every man. The man can exist whether the clothing suits his figure or not, but he is not garbed to the best advantage. In the same way one method of treatment may bring a certain patient through the illness, but not in the easiest or best way. It seems to me that the importance of drilling this fact into our students should be more realized by those of us who are teaching therapeutics—and every clinical teacher must consciously or unconsciously be teaching something about the care of the patient—for there would be less of rule-of-thumb methods if individuality in treatment was the rule in the minds of each one of us.

DIET.

Much controversy has been waged over diet. Most of us have our own ideas and are not easily convinced that any others can be better. No matter what views

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are advanced some one will disagree vigorously, which is by no means a disadvantage. This divergence of opinion is not surprising when we consider what a protean disease this is and as much so in the ways in which it is handled as in its manifestations. Many patients will go through an ordinary mild attack with any reasonable kind of food, but I feel that in the attack of ordinary severity and in all severe attacks, the simpler the diet the better for the patient. Milk and albumin water are satisfactory, easily obtained and prepared, and cheap. We should always be careful to make certain that we are not giving contaminated milk. For the account of a good object-lesson as to the importance of this precaution a paper by Edsall[1] may be consulted. To these may be added the various modifications of milk, of which whey is specially useful, bouillon, strained gruel, ice cream, tea and coffee, and sometimes cocoa; this list really gives considerable choice. Emphasis should be laid on the value of whey in the dietary. In the conditions in which milk disagrees whey may be given with great advantage. The importance of carefully watching the stools and being guided by them as to changes in the diet should be remembered. In all cases special emphasis should be laid on the giving of large amounts of water. Let one hundred ounces (3,000 c.c.) of urine a day be the minimum to be desired, and often it is better that larger amounts than this should be passed. Consider the experience of the Lakeside Hospital in Cleveland,[2] where it was found to be a saving in the time of the nurses to have one nurse especially detailed to do nothing else than give water to the typhoid fever patients. There does not seem any evidence for the opinion held in some quarters that there is the possibility of harming the kidneys. The work of Sollmann and Hofmann[3] speaks against this. The void-

1. New York Med. Jour., 1905, lxxxi, 578.
2. Cushing and Clarke: Am. Jour. Med. Sc., 1905, cxxix, 187.
3. Am. Jour. Med. Sc., 1905, cxxix, 195.

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ing of large quantities of urine does not seem to cause the patients any disturbance. There does not seem to be any danger of giving the circulation too much work to do in handling this fluid. One should use judgment if the myocardium is weak, but in a large series of cases no evidence of overloading of the heart was found.

There are certain intestinal conditions in which there seems no question of the advantage of the simple diet. These are especially meteorism and perforation. With any tendency to tympanites, it is wise to give the simplest diet and not too much of it; when tympanites is present the diet should be reduced. Therefore, does it not seem that on the simple diet there is less chance of its appearance? I am of the opinion that liquid diet and large amounts of water are the surest preventives of meteorism. Certainly when this treatment is carried out the occurrence of meteorism is reduced to a minimum, and the best treatment of meteorism is its prevention. If perforation occurs and operation is done early, it is a great disadvantage to have the intestines distended or full of material. We can count on a certain percentage of perforations in any large series of cases, but we can not tell at the outset which ones are to perforate.

Under the heading of diet reference must be made to the so-called predigested foods, which are so extensively used. Is their use justified or to be recommended? Many of the profession by their actions answer in the affirmative and the question comes as to how much justification there is for this belief. I would advise all those who have any doubts on this subject and those who believe in the value of these foods to read with an open mind the report[4] of the Council of Pharmacy and Chemistry of the American Medical Association on them. The main objections to their use may be thus summed up:

4. The Jour. A. M. A., 1907, xlviii, 1612.

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1. They contain comparatively little nutriment.

2. They may be directly injurious from the presence of peptones or albumoses, which are of uncertain composition and may be toxic or become so.

3. The presence of alcohol in them may be harmful.

4. They are expensive.

Clinically they certainly appear in some cases to upset the stomach and cause diarrhea and distention. To give amounts of these foods which would go even a small way toward nourishing the patient, means the administration of considerable amounts of alcohol. If alcohol is to be given, it is better to give it as such and not as the constituent of one of these foods.

That any one who knows their composition can persist in considering that they have some mysterious nutritive virtue is hard to believe; and yet how else can we explain the blind belief in their value, especially when we consider that they are "drug-store" foods and may have had some time to "ripen" before being used? Their cost is a serious objection, especially when so little is obtained in return.

CARE OF THE BOWELS.

An initial purge is advised by many authorities; but is anything gained by it? It is asserted that there is an advantage in emptying the bowels. The patients who are not purged seem to do just as well—in fact, better. A study which I made of five hundred cases, in which this point was specially noted, showed that diarrhea, not only at the onset, but during the course, occurred in a much larger number of those who were given an initial purge than in those whose bowels were left alone. If the patient's intestinal tract is not disturbed and a simple diet with much water given, it is surprising how infrequently diarrhea occurs.

Constipation is to be preferred and as a rule a movement every second day is often enough. If the bowels do not move themselves an enema may be given. This

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may be the ordinary one of soap and water, or oil and glycerin may be given. It is sometimes well to give an oil enema high in the bowel through a long tube, which, if necessary, may be followed by a simple enema. The comfort of the patient must be consulted; some patients are easier if the bowels are moved every day.

THE USE OF OPIUM.

In the majority of indications usually given for the use of opium I would oppose the views laid down in many of the books. The conditions for which it is generally employed are: First, restlessness and sleeplessness; second, diarrhea; third, hemorrhage, and fourth, abdominal pain.

1. *Restlessness and Insomnia.*—Here in small doses its use is sometimes advisable, but if indicated it often seems better to give small doses of morphin hypodermically.

2. *Diarrhea.*—Here, as is usually the case in diarrhea in general, opium should be the last drug to be used, instead of the first, as is too often the case. The cause should be searched for first, for too often this is left to act and opium is given to prevent the result. An initial purge, improper feeding, the giving of beef tea or predigested foods, the use of infected milk—any of these may be the cause. The diet should be cut down to albumin water, or if milk is given it should be boiled, and sedatives, such as bismuth, may be given. If opium is needed it should be given as the starch and laudanum enema. Given by mouth, opium favors distention and conceals the most valuable symptom of perforation, abdominal pain.

3. *Hemorrhage.*—Here the standard treatment is to give opium, especially in the form of the lead and opium pill. To this treatment, although sanctioned by tradition and authority, I would take exception. The advantage is claimed for it that peristalsis is lessened. Have we any proof that this is an advantage? It may

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lessen the chance of a clot being dislodged, but when we think how rarely a clot is found at autopsy in patients who have died after hemorrhage, the importance of this does not seem great. Against the use of opium there are several points. It increases the chances of distention, in itself a serious matter. In the case of gastric ulcer, distention increases the chance of perforation and the same is probably true of the bowels. Then in a considerable number of cases hemorrhage and perforation occur together. Give opium for the hemorrhage and we know the end. It comes painlessly, but surely. Any one who has been called in consultation to decide as to the possibility of perforation in a patient who has had large doses of opium, knows how hopeless it is to give any opinion. Then, too, the giving of large amounts of opium seems to have an injurious effect on the general condition of the patient.

4. *Abdominal Pain.*—Under no circumstances should opium be given, for this is our chief aid in the recognition of perforation. The men who treat many patients with typhoid fever and say that they never have perforation probably do one of two things, perhaps both (possibly it would be better to say they do one and leave the other undone); they give opium or do not have autopsies.

The first thing in the treatment of abdominal pain is to determine the cause. Evidently if it be due to a distended bladder, meteorism or impacted feces, we are not going to help matters, but rather make them worse, by giving opium. If the cause can be found the indications are clear; if it can not be found we must not give a drug which prevents our determining the cause, certainly in the more serious conditions. When the cause is not determined—and these cases are not very rare—simple measures, such as the application of stupes or small doses of bromid of potassium or codein may be enough. If the pain is not relieved by these, it

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may be necessary to give a small dose of morphin hypodermically (gr. 1/8), which is always to be preferred to opium. In this dosage it is not likely to mask abdominal symptoms.

HEMORRHAGE.

There seems no doubt that the use of the calcium salts, preferably the lactate, is helpful. In hospitals, or elsewhere when possible, it is well to take the coagulation time of the blood when the patient comes under observation. If this be prolonged it is well to give the calcium lactate as a prophylactic measure. Too large doses should not be given; probably twenty grains a day is enough. In case of hemorrhage the drug should be begun at once and thirty grains a day may be given. When it is important to obtain a rapid action the calcium lactate may be given subcutaneously in a 1 per cent. solution. The use of astringent drugs, such as lead acetate, or the giving of ergot, does not seem to be of any use and the latter is perhaps harmful. Quiet is essential and if the patient is restless this may be secured by a small dose of morphin (gr. 1/8) hypodermically. it is well to limit the amount of food by mouth, reducing the diet to albumin water or sometimes to water alone.

To keep the patient quiet, to limit the intake, to apply a light ice-bag to the abdomen, to give the calcium salts, not to give opium, and not to try to do too much, seem the main points in the treatment of this complication, which after all is not usually as dangerous as has been thought.

PERFORATION.

How many of the five thousand[5] patients every year in the United States in whom perforation occurs are saved and how many should be saved? If those two figures do not correspond, where is the blame? To de-

5. This is, of course, only a general figure. The actual number is probably much greater.

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termine how many should be saved is difficult, but it is a question whether we are sufficiently awake to the frequency of perforation, or to the importance of its early recognition and treatment. There is no doubt of the much greater difficulty in diagnosis and treatment when patients are treated at their homes than when they are in a hospital. Still, even here it would seem that much more might be done. To make an early diagnosis of perforation, preparations must be made beforehand. As a rule the diagnosis does not force itself on the careless observer. The lesson of the importance of prompt cooperation between the medical and surgical sides has been learned in many hospitals, but there are still some in which more attention might be given to this. The early recognition of this complication is as much a matter of treatment as anything else.

DISTENTION OF THE STOMACH.

While we are all aware of distention of the intestines, it is not so generally recognized that distention of the stomach is by no means rare. It may give considerable distress and affect both the respiration and the action of the heart. The passage of a stomach-tube gives immediate relief and no hesitation need be felt in doing it. The tube can be passed without raising the patient's head. It is well to cut down the diet to albumin water and to repeat the passage of the stomach-tube as often as necessary.

ALCOHOL.

The indications for the use of alcohol are much disputed and some of our extreme friends hold that its use is never justified. Certainly its routine use is not to be advised. I consider that the best indication for its use is toxemia. In some way or other the toxic patient can use alcohol, whether we consider it a stimulant or a food. When it is being given care should be taken to use a good variety, just as we make sure that the milk is

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good. The amount must be decided by the needs of the patient. Generally, when it is indicated, good doses are advisable, from six to twelve ounces in the twenty-four hours; two or three ounces in the same period are usually not enough. The statement is still repeated at times that the patient who is being given tub baths needs alcohol. This is by no means the case—quite the contrary. The patient who is receiving the tub treatment, as a rule, requires less alcohol, as toxemia is so much diminished. Alcohol does not require to be given merely because the patient is having baths.

HEXAMETHYLENAMIN.

When we remember the frequency of bacilluria and the very common presence of typhoid bacilli in the gall bladder, it seems wise to suggest the administration of hexamethylenamin (urotropin) to every patient. The work of S. J. Crowe,[6] who has shown that when this drug is given in sufficiently large amounts (75 gr. per diem) it appears in the bile in quantities sufficient to have a bactericidal action, proves the value of this. He also found that hexamethylenamin was present in the cerebrospinal fluid, synovial fluid, saliva, pleural effusion and blood. How much "killing out" of typhoid bacilli we can do by this means is as yet undetermined, but certainly these findings are suggestive.

The question arises as to the safety of giving such an amount of this drug (75 gr. per diem) to patients as a routine. There are reported instances[7] of hematuria following its administration. These are comparatively few, but further observations are necessary before positive statements can be made. With the number of patients of all kinds who are taking this drug it should not be long before we have definite statistics from a large number of observations. Painful micturition

6. Johns Hopkins Hosp. Bull., 1908, xix, 109.
7. Coleman: Med. News, New York, 1903, lxxxiii, 393.

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sometimes occurs, but it is not serious and disappears rapidly after stopping the drug.

Certainly in view of the fact that smaller doses (gr. 30 to 40 per diem) apparently prevent bacilluria, we should not hesitate to give these to every patient.

SEROTHERAPY.

It does not seem possible at the present time to speak with certainty as to the value of any of the various serums which have been used. The results claimed by Chantemesse are excellent, but have not been sufficiently verified by other observers.

PREVENTIVE INOCULATION.

While this has proved of some value in military medicine, especially when troops were to be sent to infected localities, yet the results have not been strikingly successful. That it can be of much value in ordinary practice seems doubtful, especially when we remember that it is not wise to employ it during the time of an epidemic, owing to the temporary increase in susceptibility following the inoculation. The "man in the street" is not likely to be willing to undergo it at other times.

THE PREVENTION OF INFECTION.

It is to this that we must devote more care than we have in the past. We quite understand what a man means if he says that he has attended ten patients who were seriously ill and brought them all through safely. But if he announced that he had attended ten patients without a single case of infection from them and no danger of infection in the future, we should wonder at first what he meant. Yet the second statement means more to the community and represents a great deal more thorough and commendable treatment than the first. It often requires care and brains and hard work to pull a patient through the attack, but it needs more of all three to ensure that he does not pass his infection on to some one else.

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The work of recent years has brought to our notice certain methods of transmission which may be emphasized. One is the importance of contact infection. How much this means through the country may be guessed at perhaps by the number of cases which occur in our hospitals. "Accidents occur in the best-regulated families," but altogether too many "accidents" of this kind occur in our best-regulated hospitals. In reference to this point, an excellent study is that by D. L. Edsall,[8] which should be read by all those interested in the subject. The report of the Commission for the Study of Typhoid Fever in the Spanish-American War (Reed, Vaughan and Shakespeare), did much to bring out the importance of contact infection.

Another method is what may be termed intermediate contact, in which the bacilli are carried by flies. How difficult this is to prevent perhaps the country practitioner can tell better than his city confrère. Unfortunately we all know it. Then there are the so-called "carriers," who go about with a supply of typhoid bacilli which are being constantly distributed.

HOSPITAL TREATMENT.

When we turn to the question of the prevention of infection and the carrying out of the proper measures, we realize the tremendous difficulties involved. Until recently the custom in Britain of sending patients with typhoid fever to special hospitals seemed rather unnecessary, but we have learned how wise such a plan is. There seems no question of the necessity of our introducing very much greater care and more stringent regulations in handling the patient with typhoid fever.

In view of the constant occurrence of instances of infection in hospitals the need of greater care requires no emphasis. The other patients, nurses, orderlies and physicians are all exposed to this risk. Precautions

8. Am. Jour. Med. Sc., 1908, cxxxv, 469.

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which we should endeavor to carry out are discussed under various headings.

a. Isolation.—Should a typhoid patient be isolated in a special ward? Undoubtedly whenever possible this measure should be carried out. In many hospitals in the ordinary incidence of the disease it seems almost impossible; there is neither the ward accommodation nor a sufficient number of nurses to carry it out. Yet we should endeavor to do it as far as possible. The typhoid fever patients should be kept together in one part of a large ward or as far as possible in one part of the hospital. Every effort should be made to have special nurses and orderlies waiting on these patients alone. The question of a separate kitchen and food supply is also important. The diet for the typhoid patients is so simple and the dishes they require are so few that it is not a difficult matter to keep these separate. One rule should be absolutely enforced—the nurses and orderlies who are waiting on the typhoid-fever patients should have nothing to do with the preparation of the food for the other patients. Too often a nurse goes directly from waiting on a patient with typhoid fever to prepare food for the other patients in the ward, or an orderly may be handling the ice for the water-cooler.

b. Physicians.—It should not be necessary to point out the necessity for care on their part, both for their own sakes and for that of the patients. It requires constant attention always to remember to wash the hands after examining a patient with typhoid fever before going on to a patient with another disease, and yet undoubtedly there is the risk of infection if this is not done. For both physicians and medical students the need of care in the examination of the urine and stools from typhoid fever patients should be kept in mind.

c. Nurses.—The frequent occurrence of typhoid fever among nurses suggests that the care usually taken

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is not sufficient. To reduce or prevent this infection is difficult. Careful instruction as to the danger, strict regulations as to disinfection, and thorough oversight to ensure that these regulations are carried out, are all important. One difficulty is that the nurses often have too much to do. This is especially apt to be the case with the night nurses. Disinfection after each handling of a typhoid-fever patient means time, and this the nurse on a heavy ward may not seem to be able to spare. Whenever possible the nurses attending to the typhoid patients should do that alone. The wearing of rubber gloves should reduce the danger of infection. They could be used for the greater part of the work done, especially that connected with the changing of clothing, handling of bed pans, urinals, etc. In giving sponge or tub baths their use is not so important.

d. Orderlies.—It has always been a surprise in the Johns Hopkins Hospital that so few of the orderlies contracted typhoid fever. In any hospital they must always be regarded as likely means of carrying infection; being usually overworked, apt to be careless in any case and thoughtless about danger, they require constant watching. Even with stringent regulations, it is hard to be sure that orders are obeyed. There is no doubt that as much as possible of the waiting on typhoid-fever patients should be done by the nurses. Strict oversight and great care in the handling of the ward utensils are most essential points.

e. Ward Utensils.—These should be rigidly isolated. The bed pans, enema nozzles and urinals should be kept for the use of the typhoid-fever patients only. The thorough disinfection of these is most important. Edsall mentions in the article already noted an apparatus devised by Dr. C. P. Noble in which the bed pans can be boiled. The urinals and nozzles should be boiled and kept in an antiseptic solution. The same rules as to isolation and disinfection should apply to the thermometers. These measures are important, not

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only for the protection of other patients, but also for that of the nurses and orderlies.

f. Food.—No one who is handling typhoid-fever patients should be allowed to have anything to do with the food supply for the other patients. In almost all hospitals this is difficult to carry out, but it should be done. If a patient with smallpox was concerned, there would be no doubt of this being carried out, but we are accustomed to typhoid fever. The easy possibility of food infection was well shown by an instance which came under my observation. A patient who had a chronic cystitis due to the typhoid bacillus, anxious to be of some help in the ward, was found to have been giving water, into which he had put pieces of ice, to other patients. Luckily no infection followed.

g. Flies.—Here is a problem difficult of solution. The easiest way is to keep the flies from the typhoid-fever patient. By screens the number in a ward can be kept to a minimum, and by keeping netting over the patient the chances of the flies in the ward getting at him are reduced. Even with screens it is difficult to keep the flies away when necessary things are being done. Care should be taken to prevent flies from lighting on the dejecta before these are sterilized, and the bed pans should be covered, especially as they are sometimes left standing for some time before being sterilized.

h. Disinfection of Stools and Urine.—The methods for this need not be discussed here. The important thing is to see that they are carried out. For this, constant oversight is necessary, especially of the orderlies.

PRIVATE PRACTICE.

Here the problem of prevention of infection may be much easier or almost impossible of solution. In a wealthy home, with two trained nurses, there is not very great difficulty. The rules of the hospital can be carried out rigidly. But in the homes of the poor it is quite another matter. The mother of a large family

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may have to nurse the patient and attend to the rest of the family. Take some of the conditions one finds. The patient is nursed by one of the family, possibly well-meaning but ignorant; flies are numerous, both about the patient and on the food; the urine and feces are perhaps thrown out on the ground in the country or in the ordinary privy, the flies being there also. Who can feel any certainty of being able to prevent infection under such circumstances?

Still, much may be done. The danger of infection should be emphasized every day, and, if possible, those waiting on the patient prevented from preparing the food for the family. Specific written directions as to the rules of isolation and disinfection should be given. These should be put under the headings: (1) for the attendants, (2) for the food utensils, (3) for the clothing, sheets, bed pans, etc., and (4) for the urine and stools. The physician should himself demonstrate how the dejecta are to be handled. It should be possible to prevent them from being thrown out on the ground or into an open privy, whether thoroughly disinfected or not. The possibility of infection of a water supply must always be remembered. To keep flies away it is usually possible to have the room screened. If wire screens can not be obtained, cheese-cloth can be put over part of the window to hinder the entrance of flies. Netting can also be used over the patient.

PRECAUTIONS IN CONVALESCENCE.

It is the duty of every man who treats patients with typhoid fever to take every means in his power to be sure before the patients are discharged that they are not typhoid "carriers." This is easy as regards the urine, but very difficult as regards the stools. To every patient urotropin should be given during the course and in convalescence. By doing this we can be reasonably sure that the urine is free of bacilli, and by giving large doses (75 gr. per diem) we may do much

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to destroy them in the gall bladder. In doing this we should watch constantly to avoid the production of hematuria.

Certainty as to the stools being free of bacilli is difficult to attain. Even in hospitals this may seem impossible. It is a large question and perhaps will have to be a matter of inspection by the state. To hope for this may seem utopian and yet it should come. It would be done in case of plague, but that is an unfamiliar story to us; typhoid fever is an every-day matter and familiarity brings carelessness.

There is no question of the difficulties that meet us when we endeavor to make sure that no other individual stands in any danger of infection from our typhoid-fever patients. It is so easy to rest content with bringing the patient through the attack; that is something which shows and there is no applause for the prevention of cases of typhoid fever which might have been. Yet if the statistics of any community show a decreasing incidence of the disease, every practitioner in it who has done his part to bring this about can have the consciousness that to him belongs some of the credit. Must not this be the highest reward for many of the triumphs of preventive medicine?

807 St. Paul Street.

DISCUSSION.

DR. ALEXANDER LAMBERT, New York: Feeding experiments were carried out under my care a year ago on a number of patients. In giving a diet absolutely free of milk, in which sugar was abundant, a remarkable point was the absolute lack of meteorism; the abdomens were excavated instead of swollen, the delirium diminished rapidly, the patients were clear-headed, required no medication and lost weight to a small extent. One boy went two and a half weeks with a loss of about five pounds in weight. Dr. McCrae's stand as to diet is the stand of the famous old woman who said that she was always open to conviction, but she would like to meet any one who could convince her. I think that if Dr. McCrae will leave out the milk he will be convinced that there is a better diet and a most generous one, of rice, broth, sugar, butter and a few crackers; it will open his eyes to the possi-

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bilities of a diminution in the toxicity of typhoid fever, a diminution of the delirium and meteorism in the majority of patients.

Dr. H. B. Weaver, Asheville, N. C.: It is said that there are lies, exaggerated lies, and statistics. I should hate to give my statistics in reference to typhoid, but my experience has given me some positive ideas regarding the treatment of typhoid with what I call a mixed diet. My plan of treatment is to begin the case with a mild laxative, of calomel, not with the German rule of heroic doses of calomel. After the alimentary canal is cleared then I begin with plenty of water on the inside, and when hyperpyrexia arrives with plenty of water on the outside. As to the diet, I give enough milk, if well borne, with plenty of chicken broth with rice cooked in it, and a few crackers now and then. This will suffice for all cases of typhoid fever. In reference to the bowels, I never give a purgative, but rely on salt solution enemas, Nature's remedy. How do we know whether the system has enough chlorid of sodium remaining to sustain the vitality? It is said that all normally healthy persons excrete from three to four drams of chlorid of sodium daily; may it not be possible that we fail to give enough chlorid of sodium to patients during these four weeks of typhoid fever? Therefore, I mix a little salt with chicken soup and broths, which the patients take with avidity. It seems to me that they relish that food and it keeps them along to convalescence. I let drugs alone, as a rule; pay no attention to the coal-tar remedies, but rely on cold water on the outside and plenty of good water on the inside, with a mixed diet. This treatment will get a majority of patients through successfully.

Dr. E. P. Joslin, Boston: There is one point in this excellent paper to which I must take exception, and that is the recommendation for drinking excessive quantities of water and the excretion of immense quantities of urine in the twenty-four hours. Such a procedure puts a great demand on the individual. If we allow our patients eight out of the twenty-four hours for sleep, a little calculation will show that to void six quarts of urine in the remaining sixteen waking hours the bladder would have to be emptied or a glass of liquid drunk every twenty minutes.

Dr. W. S. Thayer, Baltimore: The importance of early and complete cooperation between physician and surgeon is, after all, a point which relates not only to the complications of typhoid fever, and especially to suspected cases of the bowel, but to practice in general. What one might say regarding perforation in typhoid, one might also say as well with regard to appendicitis. It is important to remember that whenever in such cases there is any thought of surgical interference we should call in our friend, the surgeon, at once. The first impulse of most conscientious physicians and surgeons

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is to avoid operation unless it is absolutely necessary, and each new man that sees the case passes through this period. I recall vividly a case in point. When I was a resident in a hospital, about fourteen years ago, at a time when early operation for appendicitis was not so common as it is to-day, I was called early one morning to see a nurse. She had an acute appendicitis. I hesitated, however, to send for the surgeon immediately, thinking that she might be better within a few hours. Two hours later I sent for the surgeon. He thought that early operation would be wise, but did not want to hurry and put it off for a few hours more. But in a few hours our minds were made up and the patient was prepared for the operation, when my chief came in and, in turn, said, "Let's wait a little while," and put it off until the afternoon. In the afternoon all were agreed as to the advisability of immediate operation, when the surgeon-in-chief arrived. The surgeon-in-chief, by a like conservative impulse, said, "Let's wait until to-morrow morning." On the following morning when the patient came to operation there was a general peritonitis, and before it was over she had three grave operations and was at the point of death. She is still living, but her life was nearly sacrificed because four conscientious men, seeing her one after another, all wanted to wait a little while; any one, had he seen the case when I first saw it, would have advised operation within an hour or two. The physician should always summon his surgical colleague the moment he suspects the eventual necessity of an operation. Such a procedure saves many lives.

Dr. Lawrence Litchfield, Pittsburg: I heartily endorse, in the main, Dr. McCrae's paper. As to calcium lactate, I even go so far as to give it hypodermically in severe cases. I have seen three cases in which large doses given hypodermically, with normal salt solution, seemed to bring very good results. I can not pass over his objection to initial purging. What he says is very suggestive, but I have the histories of over a thousand cases in which initial purging has been the rule and in which troublesome diarrheas have occurred very rarely. As to what has been said about not purging at all, I gave 150 consecutive patients daily morning doses of sulphate of magnesium, and the mortality was as low as any I ever had, and the hemorrhages and perforations were below the average. Of course, 150 cases are far too few to base conclusions on, but they are enough to show that a laxative is not a deadly thing in typhoid fever. If Dr. Ewing's position is correct, that the nitrogenous waste in typhoid fever is not from the toxins of the invading bacteria, but from autointoxication, largely from the digestive tract, it seems that a great deal might be said in favor, not only of the initial purge, but even of laxatives during the course of the disease. In speaking of flies, Dr. McCrea mentioned keeping them away from the patient

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and the food, but most important of all is to use covered bed-pans and to keep the stools away from the flies. One point as to the treatment of perforation: On account of difference in the absorptive power in different parts of the peritoneal cavity, as soon as there is a suspicion of perforation the head of the bed should be raised and kept elevated, so that there may be drainage into the pelvic cavity and not the upper part of the peritoneal cavity, which is more vulnerable. I should think it would be dangerous to roll a patient about in the search for movable areas of dulness with the effect of spreading the infection over the entire peritoneal cavity, if a leak should have occurred. As to the large amounts of water, I agree with Dr. Joslin. Of course, typhoid patients should have enough water. You remember Dr. Thayer's suggestive paper some years ago on "The Relation of Typhoid Fever to Arteriosclerosis." I think that we have all seen protracted cases of typhoid in which the radials became palpable under our very fingers. If this is true, would not the overloading of the system with so much water necessitating in extreme cases as practiced in Cleveland, the elimination of four to eight quarts during the twenty-four hours, put an unnecessary and excessive strain on the heart and favor the development of arteriosclerosis?

Dr. Henry B. Favill, Chicago: So far as I know there are only two subjects on which I am unreasonable. One is automobile scorchers and the other lead and opium in hemorrhage. There is no question about the authority, as far as authority goes, on this question of lead and opium, particularly opium, in typhoid hemorrhage. So far as my experience leads me to a judgment, it is a fact that the locking up of the bowel after hemorrhage, with opium, to which the lead is so far as it goes an additional objection, is a pernicious practice not justified by either experience or theory. Three objections exist in my mind: First, it increases the meteorism; second it tends to obstruct the excretions; third, it frequently locks in the colon a mass of blood which undergoes decomposition to such a degree that it is not to be compared with anything we meet clinically. It is a dreadful condition, hypothetically and, I think, practically, to be superinduced in a serious infective disease.

Dr. John A. Witherspoon, Nashville, Tenn.: I feel much like the boy who wrote the essay on snakes in Ireland and said, "There are no snakes in Ireland." There is no treatment of typhoid fever. I agree with Dr. McCrae when he says, let each case be its individual lesson to us. That is all right, but in his paper he did not, to my mind, carry out the idea with which he started. I heartily agree with Dr. Lambert when he condemns the use of milk, especially sweet milk, in typhoid. I believe that we would have very little meteorism, that we would have very little intestinal disturbance, if we

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properly fed our patients. Sweet milk has been, in my experience, one of the most universal disturbers both of stomach and intestines of any nourishment I have seen used in typhoid fever; therefore, I have long since ceased to use it, because every case I have demands a mode of treatment to get rid of symptoms directly produced, in my judgment, by such treatment. I believe that Dr. McCrae, who gave us an elegant way of relieving the distended stomach with the stomach tube, if he feeds his patients properly, will rarely find any necessity for using the stomach tube. You will seldom find much gas and diarrhea if you will avoid disturbing the nutrition by improper feeding of your patients. Another point on which I could not agree with Dr. McCrae is the use of hexamethylenamin to kill the bacillus in the gall bladder and elsewhere. I do not believe that it would be possible for hexamethylenamin to destroy the bacteria or bacillus typhus in the gall bladder unless you carried the treatment to such an extent that in the preparation of subjects you would practically have to prepare the dead subjects, as we would the cadaver, to kill the *Bacillus typhosus* with it. While I have had a little experience with hexamethylenamin, it has not given me the results it seems to have given Dr. McCrae. I believe in the management of typhoid fever; there can be no objection in the earliest part of the disease to the initial purge; it has been a universal practice, and I believe does aid in the future welfare of the case. Then as few drugs should be given as possible, and proper nutrition, which, in my judgment, should be egg albumins, broths with rice, etc., in buttermilk, and things of that sort will keep down the necessity for too many drugs. The fewer drugs used in this disease the fewer will be the complications. I endorse everything else in the paper, except excessive drinking of water. I do not believe that it is sensible to deluge the stomach of a patient with water or anything else.

Dr. Thomas McCrae, Baltimore: My experience has been that the large amounts of urine passed do not give any distress to the patients. The ordinary typhoid patient is wakened every three hours in the night to take nourishment and can void at that time. I agree with what Dr. Litchfield said about the advantage of the administration of calcium lactate hypodermically in some cases. In regard to the danger of overloading the circulation with water, I have never seen any evidence of it. What is it that leads to the changes in the arteries? Is it not the presence of toxins? The more we can reduce the toxemia, which you will grant hydrotherapy does, the more we reduce the danger to the blood vessels. Clinically I have not seen any evidence of harm to the circulation. Dr. Witherspoon implied that the patients in whom I had seen distention of the stomach were on a milk diet, but, on the contrary, the majority of them were being given predigested

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foods, beef tea and broths. Regarding the point about hexamethylenamin not having any effect on typhoid bacilli, it seems to me that if one point has been established it is that hexamethylenamin does kill out the bacteria in the urine. I think that this has been too definitely proved for us to have any doubt of it. In regard to the use of adrenalin in hemorrhage, I have never been able to persuade myself that it is of value either theoretically or in practical results. As to the amount of hexamethylenamin I do not think we know as yet; I mentioned 75 grains a day and perhaps we might go higher, but we have not had enough material as yet to enable us to pass final judgment. This disease has so many phases and such varied symptoms that it is natural we should have various ideas about treatment. The consoling thing is that so many of the patients recover under so many different treatments. It shows that all the truth does not rest in one method. We are all agreed, however, as to the importance of preventing infection from our patients.

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ANAPHYLAXIS INDUCED BY BACTERIAL PROTEINS.

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The discovery of the production of hypersensibility, in animals to horse serum, egg white, etc., suggested the possibility of a similar hypersensitization to other proteid materials. It was thought possible that the protoplasm of bacterial cells might lead to similar effects, and in consequence there might be danger from the employment of bacterial vaccines where for some reason the interval between a first and second dose was sufficient for the hypersensibility to develop.

In order to determine whether the foregoing conceptions were correct, a series of experiments was outlined in which guinea pigs received a small dose of a living bacterial culture which was followed, after an interval of fourteen or more days, by a second injection of the same organism.

I selected for the organisms to be employed in these experiments some of the common saprophytic bacteria so as to exclude the possibility of infection. The organisms employed were: *Bacillus cereus, B. megatherium, B. subtilis* and *B. mesentericus.* These organisms were selected because they are generally regarded as being non-pathogenic and they grow readily on the ordinary culture media, so that it is easy to secure a considerable mass of bacterial cells for injections.

The injections were always made into the peritoneal cavity, and the size of the sensitizing doses was either

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0.2 c.c. or 0.5 c.c. of a bouillon culture. The second injection ranged from 5-10 c.c. and was always administered intraperitoneally.

There were fourteen experiments with *B. cereus,* of which nine resulted in the production of what was considered as a typical reaction, and two of the results were regarded as atypical. Three of the animals died as the result of the first injection or of some intercurrent cause.

There were six experiments with *B. megatherium* in one of which there was an atypical reaction, and in one case there was induced a purulent peritonitis which terminated fatally three days after the second injection. The other four animals had rather mild symptoms (hypersensitization) from which they recovered.

There were three experiments with *B. subtilis* in one of which there was an atypical result, while the other two had severe symptoms, but subsequently recovered.

There were three experiments with *B. mesentericus* in one of which there was a typical result, while in the other two severe symptoms were developed, but the animals recovered in twenty-four hours.

There were also three experiments in which the guinea pigs had been sensitized with *B. megatherium, B. subtilis* and *B. mesentericus* respectively, and received a second injection of *B. cereus.* Though each of these animals died, as well as two normal animals injected with the same culture to serve as controls, it is evident from the symptoms and lesions that these results were due to the toxic effects of the organisms. In none of these five instances was a typical effect produced, and death resulted in from three to five hours after the injection.

Contrary to my expectations at least some of the cultures which I employed in my experiments were found to be capable of producing fatal effects, especially *B. cereus,* and hence it is impossible to be certain as to the

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as a rule, the fatal termination occurs far more rapidly in the sensitized animal than in the normal control animal, and there is also a more marked pathologic reaction in the sensitized than in the normal animal.

The results which have been regarded as typical were as follows: In a few minutes after the injection of the second dose, the animal manifests movements which indicate irritation of the peritoneal cavity, followed at times by scratching of the head and face, followed later by profound prostration, twitchings, convulsions, stupor, and death in one-half to two or three hours.

At autopsy there was at times marked subcutaneous edema, and the peritoneum, stomach and intestinal walls showed marked hyperemia, with local hemorrhages into the submucous coat of the stomach and intestines, and at times into the kidney and spleen. The peculiar nervous symptoms which these animals manifest indicate that the central nervous system is involved, and on removing the cranium the meninges are seen to be markedly hyperemic, though no hemorrhages were noticed.

The theories that have been advanced to explain the nature and cause of the hypersensitization of animals to various proteid materials are quite variable, and none appear altogether satisfying. Courmont believes that the first injection leads to the absorption of a natural protective substance and leaves the animal defenseless against a second injection. Bail believes that death is due to the production of a substance which impedes the activity of the leucocytes. Richet suggested that the phenomena are due to the presence in the proteid material of the two bodies, the one causing immunity and the other hypersensibility. Wolff believes that there is no immunity to foreign albumins of the endotoxin class, and that through the solution of the cell walls of the bacteria as the result of protective substances formed because of the first injection, the endotoxins are liberated suddenly and in large quantities. Besredka and

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Steinhardt believe that the first injection produces a brain lesion which renders the organ especially susceptible to the second injection. Currie believes that the antibody formed because of the first injection unites with the antibody-forming substances of the second injection; their union is rapid and the whole charge of the poisonous substance is freed, giving rise to sudden and severe effects.

Rosenau and Anderson state that it is probable that the first injection induces a reaction resulting in the production of antibodies, so that when the second injection is made there is probably either a union or a reaction between the antibodies and the substances in the material injected subsequently which produces the poisonous effect. Vaughan believes that proteid susceptibility and immunity are different manifestations of one and the same process. Both depend on the development in the animal body of a specific proteolytic ferment which acts on the proteid that brought it into existence. This specific proteolytic ferment stored up in the cells of the animal as a result of the first injection remains in the cells as a zymogen until activated by the second injection of the same proteid. Rosenau and Anderson[1] state that "profound chemical changes, perhaps in the central nervous system, are probably produced by the first injection of a strange proteid." Otto believes he has discovered a specific antibody in the blood serum of the sensitized animal. Gay and Southard attribute the hypersensibility to a "rest" remaining in the blood of the animal from the first injection which they designate "anaphylactin." Lewis states that the hypersensitive reaction depends on the development of a special antibody during the incubation period, which antibody may be transferred to a second animal in the blood sérum.

My experiments have been too limited in number and too indefinite in results to permit very positive state-

1. Bulletin 36, Hygienic Laboratory, U. S. P. H. and M.-H. S.

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ments as to the nature and cause of the hypersensibility. However, the definite period of incubation which is necessary for the development of the hypersensibility indicates that some form of antibody is developed as a result of the first injection which takes part in the production of the symptoms and lesions after the second injection. It seems evident that either a poisonous compound is liberated from the proteid of the second injection through the influence of the newly formed antibody or else there is formed such poisonous substance through the union of the newly formed antibody and a portion of the proteid material of the second injection.

Although I have not studied the histologic changes produced in the abdominal organs and in the central nervous system, it seems probable that the poisonous substance formed as the result of the second injection has a direct action on the central nervous system and on the sympathetic nervous system as indicated by the profound influence on the respiratory center of the brain and the pathologic effects as shown by the focal hemorrhages into the internal organs. Histologic study of these organs may throw additional light on this point.

Several attempts were made to prevent the development of the effects from the second injection by two methods; the first consisting of the etherization of the animal before administering the second dose, and the second in the employment of small doses at short intervals instead of one large dose for the second injection. Neither of these methods yielded very encouraging results, but this was probably due, in large part, to the fact that the cultures employed were possessed of some toxic properties.

No attempts were made to inhibit the effects of the second injection through the use of the serum of an animal rendered immune to the particular organism employed. It was found possible to neutralize the effects of a second dose of horse serum by the use of the

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serum of an animal immune to horse serum. I am unable to say whether the same results would follow with cultures.

The results of the investigation showed that there might be some danger in the use of second injections of bacterial vaccines when the first injection precedes the second by an interval sufficiently long for the development of the sensitizing effects. It is evident, however, that the danger under these conditions would be very remote because the dosage of bacterial vaccines employed ordinarily is too small to be dangerous.

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DISCUSSION.

DR. VICTOR C. VAUGHAN, Ann Arbor: I object to the term anaphylaxis. Anaphylaxis means decreased protection, and it seems to me this is overprotection rather than decreased protection, because, as all the work done along this line shows, the second dose must be, as compared with the first, quite an appreciable quantity.

DR. D. H. BERGEY, Philadelphia: The cultures I employed were presumably non-pathogenic, but if I were to do the work over again I would use cultures that were killed by some means so as not to produce infection, that I might use the full organism and not the proteid from the organism. That is an important criticism of my work, and I should be guided by it in continuing it.

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SERUM DIAGNOSIS OF SYPHILIS.

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The investigations of Bordet and Gengou first directed attention to the possibility of determining the presence of antibodies by an indirect method known as complement deviation. By this means not only could bacterial antibodies be determined, but likewise their corresponding antigen. (The latter term is applied to any bacterium or substance which, when injected into an organism, gives rise to the formation of an antibody.)

It was found by this method that organ extracts, albumins, peptones, etc., produce antibodies, and that this could be shown *in vitro* by bringing together the antigen and its corresponding antibody in the presence of complement. The anchoring of complement was demonstrated by failure of hemolysis to occur in an added inactivated hemolytic system.

Wassermann and Bruck used this method to show the presence of bacterial substances in organ extracts and corresponding antibodies in sera of patients immunized against them. They employed this method with considerable success in typhoid, tuberculosis and meningitis epidemica.

It occurred to Wassermann that this principle might be applied to demonstrate antibodies in the sera of syphilitics. With this in mind he, with Neisser and Bruck,[1] began a series of investigations.

1. Wassermann, Neisser and Bruck: Deutsch. med. Wchnschr., 1906, xxxii, 745.

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Their first experiments were made with monkeys. They obtained immune sera by injecting into monkeys extracts of syphilitic organs or lesions procured from syphilitic monkeys or human beings. They afterward mixed the immune serum of the prepared monkey with the extract of syphilitic organs obtained from a dead luetic new-born, added complement, and found that in many instances a fixation of complement occurred, whereas it did not occur when mixed with similar extracts of normal organs nor when normal serum was mixed with syphilitic or normal organ extracts.

They looked on this as a means of demonstrating *in vitro* syphilitic antibodies in the blood serum and syphilitic substances in the organs of luetics.

The first clinical application of this method was reported by Detre,[2] who found specific antibodies in the blood of two out of six luetics he examined.

The examination of 257 specific cases in the dermatologic clinic of Breslau reported by Neisser, Bruck and Schucht[3] showed positive results in only 19 per cent. Their experiments were conducted also with a view of demonstrating antigen, which they found in extracts of blood corpuscles of luetics in a much larger percentage.

The above results have never been quite clear, as they were entirely out of accord with the results of all other investigations and likewise of Bruck's[4] later work in company with Stern.

Wassermann and Plaut[5] examined the spinal fluid of forty-one progressive paralytics and obtained a positive reaction in 78 per cent; nineteen controls, whose spinal fluid was examined, all gave negative results.

Schutze[6] examined twelve tabetics and found antibodies in the spinal fluid of eight. Morgenroth and

2. Detre: Wien. klin. Wchnschr., 1906, xix, 619.
3. Neisser, Bruck and Schucht: Deutsch. med. Wchnschr., 1906. xxxii, 1937. Wassermann, Neisser, Bruck and Schucht, Ztschr. f. Hyg., xlv, 45.
4. Bruck and Stern: Deutsch. med. Wchnschr., 1908, xxxiv, 459.
5. Wassermann and Plaut: Deutsch. med. Wchnschr., 1906, xxxii, 1769.
6. Schutze: Berl. klin. Wchnschr., 1907, lxiv, 126.

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Stertz[7] obtained a positive reaction with the spinal fluid of eight paralytics and a negative reaction with the lumbar fluid of eight control cases.

Marie and Levaditi[8] confirmed the findings of Wassermann and Plaut by reporting a positive reaction with the spinal fluid of 73 per cent. of thirty-nine paretics, four out of five tabetic paralytics, and two out of four tabetics. They had negative results in a number of controls among cases with diseases of the nervous system not depending on syphilis.

These investigations served to clinch the etiologic association of progressive paralysis and tabes with syphilis.

Although Wassermann first believed this test to be a reaction between luetic antibodies and syphilitic substances contained in the luetic organ extract, it became evident to those working with the reaction that this was not the case.

Attention was attracted to this by Marie and Levaditi, and confirmed by Fleischmann, Michaelis and others. Levaditi observed that with normal liver extract some delay in hemolysis occurred and that when the normal extract was used in larger quantities a strong anticomplement reaction occurred. A parallel anticomplement reaction was not noticed when the luetic and normal extracts were used in the same proportions.

Levaditi, however, considered the reaction, in view of his negative results in control cases, specific for syphilis.

Weil,[9] following the observation of Levaditi, attacked the specificity of the test. He experimented with extracts of tumors (sarcomas) which he used instead of luetic liver extract, and obtained a positive reaction with syphilitic sera, the same as had been obtained with extracts of normal organs when used in similar quantities. Kraus asserted that he, with Volk, had reported this

7. Morgenroth and Stertz: Virchow's Arch. f. path. Anat., 1907, clxxxviii, 166.
8. Marie and Levaditi: Ann. de l'Inst. Pasteur, 1907, xxi, 138.
9. Weil: Wien. klin. Wchnschr., 1907, xx, 527.

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observation with regard to normal organ extracts before Levaditi.

Michaelis[10] confirmed the work of Levaditi, and held the reaction specific for syphilis.

Landsteiner, Müller and Pötzl,[11] in their investigations, used extracts of guinea-pig liver as antigen. They compared the results of this in the reaction with luetic liver extract and found that they coincided.

Since it has become clearly evident that the active constituents of the extracts concerned in the reaction do not consist of luetic substances, to-wit, *Spirochaeta pallida* of Schaudinn, numerous experiments have been made and are still going on to determine their identity.

Wassermann,[12] with Porges and Meier, Landsteiner, Müller and Pötzl,[13] Levaditi and Yamanouchi,[14] independently of each other, made extracts of syphilitic and normal liver with alcohol and found that such extracts contained the antigen and served for evoking the reaction. Landsteiner used alcoholic extracts of guinea-pig heart and showed that results were obtained similar to those obtained with luetic liver extract.

This observation of Landsteiner, Müller and Pötzl is of great practical importance and will prove of immeasurable advantage in promoting the use of the Wassermann reaction because of the readiness with which guinea-pig's heart can be secured and prepared.

In view of its solubility in alcohol, Wassermann thought that the active constituent must be closely allied to the lipoid bodies. With this in mind, Porges[12] and Meier, under Wassermann's direction, experimented with lecithin and, in fact, found that it caused a deviation of complement with luetic sera.

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10. Michaelis, L.: Berl. klin. Wchnschr., 1907; lxiv, 1103.
11. Landsteiner, Müller and Potzl: Wien. klin. Wchnschr., 1907, xx, 1565.
12. Wassermann: Berl. klin. Wchnschr., 1907, lxiv, 1599.
13. Landsteiner, Müller and Potzl: Wien. klin. Wchnschr., 1907, xx, 1564.
14. Levaditi and Yamanouchi: Compt. rend. Soc. de biol., 1907, lxii, 741.

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This has led to investigations with other substances, cholesterin, glycogen, sodium taurocholate and glycocholate, vaselin, etc.

Levaditi found lecithin and the sodium salts of the bile acids to work satisfactorily. Fleischmann[15] found cholesterin more satisfactory, compared with the luetic liver extract, than the lecithin.

I have employed both lecithin and cholesterin, using guinea-pig heart extract as control in the reaction with luetic sera. My experience is as follows:

I examined eleven syphilitic sera with extract of guinea-pig heart and with lecithin. Eleven were positive with the extract and ten with lecithin. The intensity of the reaction with the same serum varied somewhat as between the extract and lecithin. In six the reaction resulted alike. In two the reaction with extract was more marked and in two more marked with lecithin.

Seven syphilitic sera were examined with both extract of guinea-pig heart and cholesterin. Seven were positive with extract and six with cholesterin. The result of reaction was alike with both in four cases. In two cases the extract gave a more marked reaction than cholesterin.

In the search for the active chemical constituent of the extracts Sachs and Altmann[17] used sodium oleate as antigen and obtained positive reactions with syphilitic sera. Continuing their experiments, Sachs and Altmann[18] found that they could prevent the reaction between luetic sera and alcoholic extract of luetic liver by the addition of an appropriate dilution of sodium hydrate, and likewise in some instances could convert a negative reaction between normal sera and luetic extract into a positive reaction by the addition of properly-diluted hydrochloric acid. They came to the conclusion that either syphilitic sera differentiate themselves from

15. Fleischmann: Berl. klin. Wchnschr., 1908, lxv, p. 490.
17. Sachs and Altmann: Berl. klin. Wchnschr., 1908, lxv, 494.
18. Sachs and Altmann: Berl. klin. Wchnschr., 1908, lxv, 699.

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other sera by a lessened alkalinity, or that (which they considered more likely) the special quality of the syphilitic sera is to be sought in another factor, for the reaction of which, with the lipoids, the diminished alkalescence is necessary.

Following close on the experiments with lecithin as antigen in the syphilis reaction, Porges,[19] in company with Meier, worked out a modification of the serum diagnosis for syphilis. They found that luetic or metaluetic sera precipitated lecithin from solution. The test consists in mixing equal parts of a 0.2 per cent. suspension of lecithin in distilled water and serum of a suspected patient in a test-tube and incubating for five hours. If it is a syphilitic serum, a flocculent precipitate forms. Kraus, in discussing the subject at the time, asserted that the specificity of the Porges test was supported by the experiments of Eisler. Nobl and Arzt[20] shortly thereafter published their results of the Porges reaction. They examined eighty-three cases and found a positive reaction in 81 per cent. of them.

Fritz and Kren's[21] investigations of the Porges reaction showed that while it was positive in 63 per cent. of fifty-one cases of manifest syphilis, it was also positive in 65 per cent. of seventeen cases of tuberculosis of the lungs and skin that they examined. Using sodium glycocholate in place of lecithin in twenty-six cases of syphilis they obtained positive results in 65 per cent., while they obtained only 18 per cent. of positive reactions with this salt in tuberculosis.

The complete shattering of the specificity of this test is found in the report of Eisler,[22] whose results Kraus[23] had apparently misinterpreted when he quoted them as sustaining the specificity of the Porges reaction. Eisler

19. Porges: Wien. klin. Wchnschr., 1908, xxi, 206.
20. Nobl and Arzt: Wien. klin. Wchnschr., 1908, xxi, 287.
21. Fritz and Kren: Wien. klin. Wchnschr., 1908, xxi, 386.
22. Eisler: Wien. klin. Wchnschr., 1908, xxi, 422.
23. Kraus: Wien. klin. Wchnschr., 1908, xxi, 206.

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reports that precipitating and non-precipitating animal sera give the lecithin but not the Wassermann reaction, and that sera of tuberculosis cases give it in about the same proportion as cases of syphilis.

Porges and Meier[24] have recently published the results obtained in the examination of 100 syphilitic sera by means of the watery extract, the alcoholic extract of luetic liver, the lecithin suspension and by their method of precipitation with lecithin. They found the results of the lecithin reaction to run parallel to those obtained by the complement fixation method.

Another modification in the serum diagnosis of syphilis was presented by Klausner,[25] who reported that on mixing one part of serum with three of distilled water and allowing it to stand at room temperature a flocculent precipitate formed in from one to fifteen hours.

In a subsequent report by Klausner[26] he states that in his controls he obtained positive reactions in five severe lupus cases, five typhoid cases and three cases of pneumonia. The reaction depends on the precipitation of globulin which is increased in infectious diseases. It would seem to lack specificity for syphilis.

Parallel tests carried out by me with the Wassermann, Porges, and Klausner reactions gave the following results in nine cases of syphilis:

	+	−
Wassermann reaction	9	0
Porges "	6	3
Klausner "	2	7

Although we are apparently closer to a solution of the theoretic basis of the Wassermann reaction, any final statement at this time would seem, from the experimental results so far recorded, unwarranted.

It would appear from the evidence at hand that there is some substance in the sera of syphilitics not contained in non-syphilitic sera which has an avidity for certain substances contained in luetic and normal organs, and

24. Porges and Meier: Berl. klin. Wchnschr., 1908, lxv, 731.
25. Klausner: Wien. klin. Wchnschr., 1908, xxi, 213.
26. Klausner: Wien. klin. Wchnschr., 1908, xxi, 363.

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also in guinea-pig organs, and for certain lipoid bodies, as lecithin, cholesterin, etc. (Wassermann).

After this extended consideration of the development and theoretic basis of the serum reaction I shall take it up in its practical aspect.

The specificity of the test is a matter of paramount importance from a practical standpoint. Fortunately the statistical proof now before us from different and reliable sources is sufficient to establish the specific character of the reaction.

In practically every case the controls examined by various investigators have proved negative. Even Weil, who attacked the specificity of the reaction in the first instance, and later with Braun the specificity of the antigen, was not able to secure the reaction with non-syphilitic sera. At the same time their results with syphilitic sera bespeak its specificity.

Following are some of the results of examinations recorded:

DETRE[5] obtained positive reactions with the sera of 2 out of 6 luetics.

WASSERMANN AND PLAUT[6] examined the spinal fluid of 41 paralytics; 78 per cent. of the reactions were positive. They also examined 19 controls; findings all negative.

MORGENROTH AND STERTZ[7] examined the spinal fluid of 17 paralytics and metasyphilitics; 53 per cent. of the reactions were positive; in the spinal fluid of 8 controls, the findings were negative.

MARIE AND LEVADITI[8] examined the spinal fluid of 39 progressive paretics; 74 per cent. of the reactions were positive; in 5 tabetic paralytics, 80 per cent. of the reactions were positive.

CITRON[27] examined 108 cases of evident or suspected syphilis; 74 per cent. of the findings were positive.

FLEISCHMANN AND BUTLER[28] examined 41 syphilitics and suspected luetics; in 70.7 per cent. of the cases the findings were positive.

MICHAELIS[10] examined 12 cases of certain and suspicious lues; 75 per cent. of the reactions were positive; of 23 controls, 2 reactions were positive.

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27. Citron: Deutsch. med. Wchnschr., 1907, xxxiii, 1165.
28. Fleischmann and Butler: THE JOURNAL A. M. A., 1907, xlix, 934.

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M. WASSERMANN AND MEIER[29] examined 39 suspicious cases; 69 per cent. of the reactions were positive.

SCHUTZE[9] examined 12 cases of tabes; 75 per cent. of the reactions were positive.

FISCHER AND MEIER[30] examined 114 syphilitics; 83.7 per cent. of the reactions were positive.

MEIER[31] examined 118 cases of lues; 81.7 per cent of the reactions were positive; in 21 controls all the findings were negative.

KRONER[32] examined 40 cases of suspected lues; 75 per cent. of the reactions were positive; in 10 controls all the findings were negative.

MÜHSAM[33] examined 80 cases; obtained positive results in 48. All of the latter proved syphilitic by examination or as the result of treatment.

KAREWSKI[34] examined 18 suspected cases; the reactions were all positive.

WEIL[9] examined 9 luetics; 88 per cent. of the reactions were positive.

WEIL AND BRAUN[35] examined 15 metasyphilitics; 80 per cent. of the reactions were positive; of 7 controls all the findings were negative.

MICHAELIS AND LESSER[36] examined 63 syphilitics and suspected syphilitics; 74 per cent. of the reactions were positive.

MÜLLER[37] examined 197 cases of syphilis; 94 per cent. of the reactions were positive; of 500 controls 97 per cent. of the reactions were negative.

BLASCHKO[38] examined 270 luetics; 87 per cent. of the reactions were positive.

The varying percentage of positive reactions obtained depends on the class of cases examined. In the statistics of some writers, cases with manifest symptoms dominate; in others, metasyphilitic and latent cases make up a good share.

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29. Wassermann, M., and Meier: Deutsch. med. Wchnschr., 1907, xxxiii, 1287.
30. Fischer and Meier: Deutsch. med. Wchnschr., 1907, xxxiii, 2169.
31. Meier, G.: Berl. klin. Wchnschr., 1907, xxxiii, 1636.
32. Kroner: Berl. klin. Wchnschr., 1908, xxxiv, 149.
33. Mühsam: Berl. klin. Wchnschr., 1908, xxxiv, 14.
34. Karewski: Berl. klin. Wchnschr., 1908, xxxiv, 15.
35. Weil and Braun: Berl. klin. Wchnschr., 1907, xxxiii, 1572.
36. Michaelis and Lesser, F.: Wien. klin. Wchnschr., 1908, xxi, 289.
37. Müller: Wien. klin. Wchnschr., 1908, xxi, 282.
38. Blaschko: Berlin klin. Wchnschr., 1908, xxxiv, 694.

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The uniformly negative reaction found in controls and the large percentage of positive reactions in luetic and suspiciously luetic cases not only establish the specificity but likewise the reliability of the test.

On these two points the clinical value of any blood test depends, and when they have been fulfilled, as with the serum diagnosis of syphilis, it is evident that its clinical value is settled as a diagnostic test.

Right here attention should be directed to what a positive reaction implies and what may be interpreted from it. A positive reaction only indicates that the patient has syphilis, whether acquired or inherited. Whether or not this systemic infection is the cause of a pathologic change in some organ or tissue must of necessity be learned from other clinical facts. In other words, a positive reaction may be valued as an indication of systemic infection and not used decisively in making specific organ diagnosis.

Unfortunately the performance of the reaction itself is attended with difficulties which may discourage many who undertake it. Some of these difficulties have been removed by the employment of alcoholic extracts, as the watery extracts were decidedly unstable.

The substances employed in the reaction and their preparation are as follows:

1. *Blood Serum of Suspected Luetic.*—This is obtained as follows: Collect blood from the vein or finger, allow it to clot; remove the separated serum; centrifugate to clearness; pipette off into test-tube, and inactivate at 56 C. for one-half hour.

2. *Organ Extract.*—Take luetic liver or guinea-pig heart and rub up fine with sand in mortar, add 95 per cent. alcohol in proportion of 50 c.c. to one gram of guinea-pig heart. Place in flask and heat in water bath at 60 C. for an hour. Filter through paper filter and keep at room temperature ready for use.

3. *Complement.*—Guinea-pig serum is used. Collect blood from heart of guinea-pig in sterile flask; allow to coagulate and remove the separated serum. Keep on ice ready for use.

4. *Hemolytic Serum.*—Inject a 5 per cent. mixture of washed sheep's-blood corpuscles into a rabbit every week or ten days

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for four or five times. A week or ten days after the last injection the blood may be removed from heart, serum collected, inactivated, and kept on ice ready for use.

5. *Washed Sheep's-Blood Corpuscles.*—Sheep's blood is obtained from the jugular of a sheep in a sterile flask and defibrinated by glass pearls. It is washed with salt solution two or three times and then mixed with salt solution either in the proportion of 5 per cent. or 50 per cent., according as one adheres to the cubic centimeter plan or drop method for measuring quantities.

As the serum reaction is usually performed, all constituents of test are calculated in fractions of a cubic centimeter and the quantities so diluted with salt solution that each cubic centimeter of dilution represents the desired quantity.

The suggestion of Landsteiner, Müller and Pötzl greatly simplifies this method and takes far less material. They measure the proportion of ingredients to each other by drops.

Before the actual performance of a reaction it is necessary to test material to be used:

1. To standardize the amboceptor.
2. To see that extract alone does not bind complement, or hemolyze sheep's corpuscles.
3. To see that the blood corpuscles have not hemolyzed.
4. To see that the complement is active.

The standardizing of amboceptor is effected by determining what dilution of amboceptor in a drop dose will dissolve in a half hour in an incubator one drop of 50 per cent. suspension of sheep's corpuscles with one drop of complement; a definite amount of salt solution, ten drops, is added as diluent. Twice the strength of this is used in test.

It is desirable to test the extract before each reaction is undertaken to see that it alone does not delay the hemolysis. With this point in view, a drop of extract and one of complement, in ten drops of salt solution in test-tube, are incubated one-half hour and then amboceptor and blood corpuscles are added. Hemolysis should occur within a half hour.

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If the blood corpuscles have stood for some days they may have hemolyzed, as may be judged by color of supernatant fluid.

Complement should not be used after the third day.

When all ingredients used in the test are suitable the performance of the reaction is facilitated and never disappointing.

It is necessary to introduce a few known syphilitic sera and at least as many normals in every test, these serving as controls for suspected sera.

In performing the reaction each serum is tested with and without the extract to see if in the first instance the combination inhibits the hemolysis, and in the second instance that the serum alone does not do so.

Occasionally the serum alone will hasten the hemolysis over the control in which the complement, amboceptor and blood corpuscles are contained, because of the fact that some sera possess a slight amount of amboceptor for sheep's blood corpuscles (Michaelis[10]).

The performance of the reaction is as follows:

For each serum two small test-tubes are required and several tubes for controls of the materials as above, these being repetitions of the tests of material made before beginning the reaction. Add ten drops of salt solution to each tube. Add a drop of serum to each of the two tubes used for a given serum. Then add two drops of organ extract to one of them. To one of the control tubes add two drops of organ extract. To all add a drop of complement. Shake tubes and place in incubator for one hour. Remove and add a drop of standardized amboceptor and one drop of 50 per cent. suspension of sheep's blood corpuscles. Incubate for an hour and a half and then read the result. All controls with sera alone, with normal sera, and with organ extract alone, should be hemolyzed. If in tubes containing suspected sera and organ extract hemolysis has occurred they are regarded as negative. Those containing sera and organ extract,

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in which hemolysis has not occurred at all or only incompletely, are positive.

Uncertainties not infrequently arise in reading the result of reaction. These are invariably traceable to a failure to test materials used in the reaction, failure of sufficient controls on the material, or of control sera, both syphilitic and non-syphilitic.

I have examined 125 cases. Twenty of these were controls in which syphilis could be, from examination and history, reasonably excluded. Among the control cases were typhoid, pneumonia, neurasthenia, etc., all of which reacted negatively.

Various classifications are used in reporting cases by different authors. I have grouped mine under two main heads, with subdivisions. These include:

First, cases with manifest or suspected syphilis and cases giving a history of syphilis.

Second, cases with lesions of the nervous or cardiovascular systems in which syphilis was either acknowledged, denied, suspected or unsuspected.

Of the first division there were 61 cases.

1. There were in the primary stage, either with initial lesions or before appearance of secondary symptoms, 4 cases; four positive.

2. In the secondary stage were 25 cases; 24 positive, 1 negative.

3. In the tertiary stage were 17 cases; 16 positive, 1 negative.

Of latent cases there were 15; 8 positive, 7 negative.

In the second division there were 44 cases; positive reaction in 75 per cent. Forty per cent. of these either had no knowledge of infection or denied same.

CLASS 1.—Taking up the first group of cases it will be observed that of the cases with luetic manifestations, forty-six in number, 93 per cent. gave a positive reaction. This coincides closely with the recent publications already cited for this class of cases. Some variations in percentages will necessarily result because of the method of classification used by different authors, some of whom have classed metasyphilitic cases among the syphilitic with manifest symptoms, for which there is undoubtedly

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much justification, in view of the recent light thrown on the subject by this test.

Of interest to the syphilologist is the result of this reaction in the primary stage. In a large percentage of cases with the initial lesion, this reaction is found positive. This is of great value, not only in analyzing a venereal infection, to-wit: chancroid with possible chancre, urethral chancre, etc., but it is of immense advantage from a therapeutic standpoint, deciding the diagnosis in many instances at once, in case any doubt existed from a point of view of clinical diagnosis and indicating the therapeutic course.

Attention should be directed to the advantage of this test in syphilophobia.

Of the latent cases, fifteen in number, 54 per cent. gave a positive reaction. This forms one of the interesting phases of the syphilis question developed by this reaction. Some of these patients, which number among them those that have been well treated and others indifferently treated, have been free from symptoms for a number of years.

The question whether the latent cases that are negative to the reaction may be regarded as safe and whether those that give a positive reaction are in danger of a recurrence, is of great practical importance and at the same time presents difficulties of solution not easily overcome at this time.

Recently Fleischmann[15] has reported three cases that did not give the reaction, but in which the patients within a few months had a recurrence of symptoms. He does not state how long it was from the time of the initial lesion.

The following interpretation of a negative result of the test may be considered as according with our present knowledge. The absence of reaction, even when symptoms are lacking, does not necessarily mean that the patient is cured, but simply that his infection is quiescent, but it gives no assurance beyond this point.

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While it may be rash to express an opinion as to the existing anatomic condition or destiny of latent cases, free from symptoms for a number of years, which give a positive reaction, the following statement of Lesser, made a number of years ago and recently quoted by Blaschko,[38] may be of some interest and also of value. Lesser stated that certain diseases occur in late syphilis, besides the so-called tertiary manifestations, which are not exactly to be reckoned in the gummatous affections, diffuse changes which develop slowly in apparently healed luetics and which also under circumstances can lead to death. He was able to find in about 9.5 per cent. of all autopsies, investigated by him, signs of such specific disease processes, which during life had produced no symptoms or at least were not generally diagnosed as syphilis, viz.; aortitis, etc.

On statistics collected by Blaschko and Jacobsohn, Lesser estimated that about 20 per cent. of the male population of Berlin were infected with syphilis and he maintained that the 9.5 per cent. which had shown evidences of specific processes, postmortem, represented 50 per cent. of those earlier infected with syphilis. Blaschko and Jacobsohn, from a study of insurance statistics, came to the conclusion that in one-third of the cases of syphilis, death could be traced to the disease. In luetics, therefore, syphilis is a cause of death in about 33 per cent. of the cases; but there are demonstrable changes in the organs of dead luetics in 50 per cent. of the cases, which latter percentage coincides with the percentage of positive reactions found in latent cases of syphilis.

While it would be unjustifiable at this time to draw any conclusions from this coincidence, it would seem a safe proposition that cases which give a positive reaction, even though they may not show evident manifestations, should receive serious consideration for treatment, because, irrespective, of the above statements of Lesser, it is observable in a certain proportion of the

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cases that a diminution or disappearance of the reaction will occur under treatment. Just what the latter indicates at this time with regard to cure or abeyance of the infection, no one is prepared, supported by statistics, to state.

Fleischmann and I in our first communication on this subject made note of the observation that the reaction failed in some cases under anti-specific treatment and in others that had been previously well treated, thus coinciding with Citron's observations. On the other hand we examined cases under similar circumstances that gave the reaction.

Müller[37] and Blaschk[38] and also Citron found a disappearance or diminution of the reaction in a third of their cases under treatment. In this matter the factor of time must be of importance; one patient may require a much more prolonged treatment (as is the case clinically with regard to disappearance of symptoms) to bring about a negative reaction, than is needed in another case.

This point has apparently not received any attention, namely, that the factor of time is not defined as it should be in estimating the effect of treatment on the reaction.

Just what effect antiluetic treatment may have on a patient to influence the serum reaction is a matter of conjecture.

While examining sera I tried to determine the effect of a 1-10,000 mercuric chlorid solution on various substances used in the reaction. No effect was produced on complement, amboceptor, or blood corpuscles in whatever combination used. It exerted anything but a uniform action where it was used in the reaction with the extracts.

This may be best shown by presenting results of examinations by extracts without and with mercuric chlorid solution.

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The results only are recorded under headings "extract" and "extract and mercuric chlorid solution." The number of + signs express the intensity of the reaction. I have included results of examinations with lecithin and cholesterin.

Extract.	Cholesterin.	Extract + Mercuric Chlorid Sol.
2+	1+	3+
1+	1+	—
1+	—	—
4+	2+	2+
1+	1+	1+
1+	1+	2+
2+	2+	—
	Lecithin.	
2+	1+	—
1+	1+	1+
1+	—	—
4+	4+	4+
1+	2+	—
1+	2+	1+
1+	1+	1+
1+	1+	1+
3+	2+	1+
3+	3+	3+
3+	3+	—

Reaction with extract and mercuric chlorid solution equal to reaction with extract alone 7 times.

Reaction with extract and mercuric chlorid solution stronger, 2 times.

Reaction with extract and mercuric chlorid solution weaker, 2 times.

Reaction with extract and mercuric chlorid solution abolished, 7 times, whereas with extract from 1+ to 3+.

Mercuric chlorid solution abolished the reaction in 39 per cent. of cases.

Class 2.—Following is a synopsis of the diagnosis and result of reaction:

a. Brain syphilis, 5 cases: All gave positive reaction; two of these denied luetic infection.

b. Cerebrospinal syphilis: 1 case gave positive reaction; patient gave history of lues.

c. Hemiplegia, 9 cases: 7 gave positive reaction, 2 negative. Six patients gave history of specific infection, 5 of whom gave a positive reaction. Two (no specific history obtainable) gave a positive reaction. One denied infection and gave a negative reaction.

d. Spinal lues, 3 cases: 2 gave a positive reaction. One of these denied infection. The third patient gave history of infection. Reaction was negative.

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e. Transverse myelitis: The patient in one positive case acknowledged syphilis; in one negative case the patient denied infection.

f. Case of uncertain diagnosis in which the patient gave a history of syphilis proved positive to the test.

g. Tabes, 15 cases: 8 gave a positive reaction, 7 a negative. In the positive cases 7 patients acknowledged lues, 1 denying it. In the seven negative cases 2 patients gave history of syphilis, 1 denied infection. From history of 3 others previous infection was strongly probable. In 1 no record was obtainable.

h. Epilepsy, 2 cases; in women, developed in middle life; the reaction was positive.

i. Neuritis, 3 cases: Two of the patients denied syphilis. All gave a positive reaction.

j. Vascular disease, 5 cases: All gave positive reaction. One of these with intermittent claudication, denied lues.

In the tabes cases examined by me the percentage of positive reactions is somewhat low. This class of cases, and likewise many of the other metasyphilitic cases that gave a negative reaction, are so often subjected to antiluetic treatment that it is more than probable that this is the cause of failure of reaction in some of them. Schutze found eight of twelve cases of tabes positive; Citron[27] reported thirteen of fifteen cases and Fleischmann[15] thirteen of eighteen cases positive.

A detailed consideration of cases is deemed impractical in this brief paper.

CONCLUSIONS.

The serum reaction for syphilis is specific.

It is found positive in from 90 per cent. to 95 per cent. of all cases with syphilitic manifestations.

It is found positive in 50 to 60 per cent. of latent cases.

It is found positive in from 70 to 80 per cent. of parasyphilitic diseases.

The reaction is in many cases influenced by treatment of the patient and it is not improbable that this number would be greatly increased if the reaction were pursued throughout prolonged treatment.

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A positive reaction indicates activity of the specific virus, and is an indication for antisyphilitic treatment.

While a positive reaction indicates syphilis, a negative reaction does not have an equal negative value.

It is diagnostic of a systemic infection whether acquired or inherited and not an organ diagnostic measure.

The reaction will be found of enormous advantage in differential diagnosis in every department of medicine.

DISCUSSION.

DR. KARL K. KOESSLER, Chicago: Dr. Butler says that it makes no difference whether the reaction is made with syphilitic organ extract, with an alcoholic extract of a normal rabbit's heart, or with lecithin, according to Porges and Meier. I can not confirm his opinion. Although the Porges-Meier reaction is said to work with lecithin only, researches made in this line at Vienna have shown that results are obtained in only 45 per cent. of cases, while the Wassermann reaction gives about 90 per cent. The Porges-Meier method, however, involves quite a different principle from Wassermann's, being a precipitin reaction having nothing to do with the deviation of the complement. Any one who, like Dr. Butler, has worked out a great many cases, knows what a long process Wassermann's method is. Certainly it would be much simpler to use the alcoholic extract instead of the syphilitic; but comparison between positive results in each method gives preference to the original procedure of Wassermann. It is perhaps better, in accord with Levaditi's modification, to use a dried extract of the liver of a syphilitic fetus, in order that it may be preserved and a solution made when needed. On account of the enormous responsibility for the physician in making the diagnosis of syphilis he should use the method which gives the greatest number of reliable results and in uncertain cases repeat the test three times at intervals of ten days and make the positive diagnosis only within the month.

DR. WILLIAM J. BUTLER, Chicago: Time would not permit the reading of that part of the paper referring to the Porges-Meier reaction. I used the Porges reaction in a small number of cases and compared it with the Wassermann and the Klausner reactions. Recent investigations show that it is not specific, because it is found that tuberculosis will give a positive reaction in about as large a number of cases as will syphilis. I did not find it positive as often as I did the Wassermann reaction in the cases of syphilis in which I used it. I notice, however, that Porges and Meier in a recent publication have compared the Wassermann and lecithin

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reactions and report almost as many positives with the latter as with the complement fixation method.

As to the relative value of alcoholic and salt solution extracts, Wassermann contends that the latter extracts give a more reliable reaction than the alcoholic. I can not say that in my own observation I have had an opportunity to compare the aqueous saline solution and the alcoholic extracts with the same sera; but it seems to me, comparing my previous experience with the aqueous extract, that the alcoholic works as well as the salt solution and it has the immeasurable advantage of being stable. I do not know of anything more difficult than to work with the salt solution extracts. They are most unreliable; sometimes in a few hours, or over night, a large quantity of liver extract will go wrong and be useless. Every test made is controlled by a series of normal and syphilitic sera. The use of these controls obviates any chance of error. If under these circumstances a suspicious serum is found positive, it can be said without hesitancy that the patient has syphilis.

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THERAPEUTIC IMMUNIZATION IN MIXED INFECTION.

A. P. OHLMACHER, M.D.
DETROIT.

Among the many problems that confront the physician who would apply in practice Wright's method of therapeutic bacterial immunization is the one of mixed infection. What should be the course in case of a mixed infection? Here, as elsewhere in the practice of bacterial therapy, judgment as to the relative importance to attach to the various factors must decide the question; and it is to give the results of my quite extensive personal experience that the present communication[1] is offered. In a general way it may be said that a mixed infection offers a less promising outlook than that by a single bacterial species, and still some brilliantly successful results have been obtained by inoculations in very complicated and long-standing infections.

Given two, or even three bacterial species, well known as pathogenic agents, and their simultaneous appearance in the secretion of a certain lesion, it is entirely proper to inoculate a mixed vaccine containing proper doses of the offending bacteria. Or when the urgency is not too great inoculation with the predominating and most

1. This condensed paper is a supplement to several previous reports which I have made dealing with the theory of opsonins and the practice of therapeutic immunization, as: A Series of Medical and Surgical Affections Treated by Artificial Autoinoculation According to Wright's Theory of Opsonins, THE JOURNAL A. M. A., Feb. 16, 1907; Practical Bacterial Therapy and the Theory of Opsonins, Ohio State Med. Jour., May, 1907; The Enlarging Field of Opsonic or Bacterial Therapy, Ohio State Med. Jour., September, 1907; and the article, Opsonic Therapy, in the forthcoming supplemental volume of the Reference Handbook of the Medical Sciences.

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likely pathogenic agent is to be first performed, and in case of an unsatisfactory issue, a vaccine from the other bacterial species can be added in subsequent injections. Say, for instance, that *Staphylococcus aureus,* or a streptococcus, is found associated with *Bacillus coli* in the discharge from fistulas of abdominal origin, a mixed vaccine would be in order. Again, especially in old suppurative lesions, a putrefactive organism (of the proteus group generally) is found largely exceeding the underlying and presumably original pyogenic agent like staphylococcus or streptococcus. Here the pyogenic microbe might first be tried, but to it should be added a vaccine from the secondary organism in event of a failure to bring a good result. I have been surprised several times to find success seemingly hinging on the use, in conjunction with the vaccine of a well-known pathogenic species, of that prepared from the secondary invader belonging to the proteus-like or colon-like, or pseudodiphtheria bacillus group, for some of these secondary organisms were clearly of saprophytic origin and one would ordinarily not assign to them any greater importance than that of accidental invasion into an already prepared soil. For example, in an extensive draining thoracic empyema which had been abandoned from the standpoint of further operative interference, and where the discharge had recently become exceedingly foul, I recovered a streptococcus and a bacillus of the proteus group. Inoculations of the streptococcus failed to effect a marked therapeutic response, but when a vaccine of the proteus was added, clinical betterment promptly began and continued until the final complete cessation of suppuration and closure of the fistula.

In dealing with the mixed infections of a pyogenic nature, it is necessary to follow the events in the more chronic suppurations by bacteriologic analyses from time to time, and to modify the inoculations to correspond with the changes in the bacterial flora of the pus in case the therapeutic response is not satisfactory.

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Certain combinations of bacterial species seem particularly obstinate in their reaction to therapeutic inoculations. It has appeared to me that chronic infection in which *Bacillus pyocyaneus* becomes associated with other pyogenic species is especially stubborn, for I have utterly failed to obtain a sustained improvement in one case of infected breast wound, and another of cystitis and possibly pyelitis in each of which the pyocyaneus was associated with the streptococcus, notwithstanding most patient trial by inoculations variously spaced and dosed, and employed both with and without the guidance of the opsonic index. Such a state of affairs is in keeping with the well-known proclivity of wounds with pyocyaneus infection to be obstinate in healing. But on the other hand, I have just passed through an experience with a recently infected phlebotomy wound with extensive cellulitis and suppuration of the arm, due primarily to streptococcus in which the widely incised suppurating tissues took on a pyocyaneus infection after a week, followed by a metastatic arthritis of the ankle due to the streptococcus alone. Here a speedy, favorable reaction followed mixed inoculations of the autogenous streptococcus and pyocyaneus, with diminution and disappearance of the blue pus in the course of two weeks and satisfactory healing of the infected incisions, including the infected joint.

In dealing with tuberculous diseases in which a mixed infection is demonstrable by the culture test it is proper to combine the inoculations of tuberculin with vaccines of one or more of the complicating bacterial species. That this procedure is conducive to good results in treating the suppurations following tuberculous urinary infection, adenitis, synovitis, or osteitis, I can add my testimony to that of other workers. It also appears to be good practice occasionally to include an inoculation of a staphylococcus vaccine with tuberculin in treating such diseases as pulmonary, glandular, joint or bone tuberculosis, even though a mixed infec-

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tion is not demonstrable. In how far the use of pneumococcus, streptococcus, or staphylococcus vaccines with tuberculin for handling the corresponding forms of mixed infection in phthisis is valuable, is a point on which my personal experience does not yet allow me to pronounce definitely.

Syphilis and a concurrent or a secondary infection with pyogenic bacteria is another condition in which therapeutic bacterial immunization finds useful application. Some of the earlier English workers in opsonic therapy found that the pus microbe infections of late secondary or tertiary syphilitic ulcers of the skin were more easily handled when inoculations of the causative bacteria were added to the specific medication. The results which I have witnessed in a rupeoid complication of a very extensive cutaneous syphilitic ulceration when inoculations of the patient's *Staphylococcus aureus* were used to reinforce the medicinal agents were such as to emphasize the value of the accessory biologic therapy. In a case in which an acute yellow pus microbe infection of a finger tip appeared as part of an unrecognized syphilitic infection of a wound received during a surgical operation, there was, aside from the ulcerating and suppurating initial lesion, a large neoplastic cellulitis of the corresponding arm, together with the constitutional symptoms of a severe septic state. I was able to control the septic condition and to effect a rapid reduction in the indurated mass by properly spaced inoculations of the autogenous staphylococcus. But healing of the ulcer of the infected finger did not occur until the advent of secondary syphilitic symptoms disclosed the nature of the underlying morbid conditions, and the proper specific medication had been instituted.

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EXPERIMENTAL PAROTITIS.

ISABELLA C. HERB, M.D.
CHICAGO.

The most noteworthy study of the bacteriology of mumps is by Laveran and Catrin,[1] who in 1893 described a diplococcus in the exudate which they obtained by aspiration of the parotid gland. They found this diplococcus 67 times in 92 cases; 39 times the organism was obtained in pure culture, twice in mixed culture, and 15 times the result was negative. The 15 negative results they attributed to the small quantity of exudate obtained. In 16 cases of secondary orchitis pure culture was obtained 12 times, once with contamination and three times they obtained no growth. The organism was obtained from the blood during the height of the fever 10 times in 15 examinations. Three times pure cultures were obtained from the edema of the overlying tissue of the gland and once from the exudate of a joint. They found it fatal in large doses to white mice. Injections into the testicle produced an inflammation which lasted about eight days.

In 1896 Mecray and Walch[2] examined the saliva from Steno's duct in 10 cases. They found a diplococcus 6 times. In 8 blood examinations they obtained the organism in pure culture 3 times, mixed with the white staphylococcus 3 times, and twice their results were negative. In 1896 Busquet and Feri examined the

*From the Pathological Laboratory of Rush Medical College and the Memorial Institute for Infectious Diseases, Chicago. This work was aided by a grant from the American Medical Association.

1. Compt. rend. Soc. de biol., 1893, v. 528.
2. Med. Rec., 1896, l, 440.

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blood and saliva in 3 convalescents and in 17 patients during the early stages of the disease and found a diplococcus in all the cases.

In 1897 Michaelis and Biem[3] examined the secretion from Steno's duct in 16 cases and obtained pure cultures of a diplo-strepto-coccus in all. Their animal experiments gave negative results.

In 1906 Teissier and Esmein[4] examined the blood in 45 cases and obtained a diplococcus in 37. The negative results were in those with a light attack of the disease or during convalescence. The organism was obtained 33 times in pure culture, twice with streptococci, twice with a bacillus and 3 times with a coccobacillus. The exudate from Steno's duct showed in 10 examinations 9 pure cultures. The coccus was fatal to guinea pigs and rabbits. Following intraperitoneal inoculations an orchitis developed in 4 of 7 rabbits. In 1907 Korentschewsky[5] isolated a diplococcus from the gland exudate in 21 of 29 cases. His blood examinations gave positive results in 8 of 32 cases. The organism was fatal to mice, guinea pigs and rabbits in large doses. No results were obtained in dogs.

So far as may be judged from the description of the investigators I have cited it appears very probable that they have dealt with the same diplococcus.

I obtained a similar diplococcus from the body of a man about 40 years old who entered the hospital in a moribund condition and died in a few hours. Except the report that he had had mumps no history was obtained. The postmortem by Dr. LeCount showed a right suppurative parotitis, bronchopneumonia and several minor lesions.

The cerebrospinal, pleuritic and pericardial fluids, bile, spleen, lung, testicle and right parotid gland were examined bacteriologically. Cover glass preparations

3. Verhandl. XV Congr. f. inn. Med., 1897, 15, p. 441.
4. Compt. rend. Soc. de biol., 1906, lx, 803, 853, 897.
5. Centralbl. f. Bakteriol., part 1, 1907, xliv, 394.

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Fig. 1.—Uniform enlargement of the left parotid gland of a dog on the fourth day after inoculation of the diplococcus into Steno's duct. The skin and muscles have been removed.

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from the bile, pericardial and cerebrospinal fluids showed a rather large diplococcus; the latter also contained a smaller coccus occurring in groups. The pleuritic fluid contained a short bacillus. They were both Gram positive. The *Proteus vulgaris* was isolated from the pleuritic, cerebrospinal and pericardial fluids, the spleen, lung, testicle and parotid gland; the *Staphylococcus albus* from the lung, testicle, cerebrospinal fluid and parotid gland. From the lung, testicle, cerebrospinal and pericardial fluids, bile and parotid gland a coccus was isolated with the following characteristics:

The coccus appears most frequently as a diplococcus, occasionally in chains of 4 to 6 elements, or in small groups. It is round and measures from .5 to .8 microns when about 24 hours old. When several days old it measures from .6 to 1.5 microns. It is easily stained by all the ordinary anilin dyes and is Gram positive. It grows equally well aerobically and anaerobically. It is not motile, has no capsule or flagella and does not form spores, gas or indol. It grows best in a temperature of 37 C. A temperature of 50 C. for three minutes destroys growth, cold inhibits but does not prevent growth when the culture is again placed under favorable conditions. Colonies developed from a milk culture two months old and from agar which was dried till it was broken. While the coccus develops on all the ordinary media, its growth is characteristically slow, the colonies on a 24-hour glycerin agar culture being scarcely visible. I have found by mixing sterilized saliva with agar, as in making blood agar, that an abundant growth is obtained in from 12 to 24 hours. Ascitic agar is also a good medium.

The organism is fatal to white mice, white rats, guinea pigs and rabbits when injected subcutaneously or intraperitoneally. The animals usually die within 24 hours of peritonitis. Those that survive for several

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days die of bacteriemia. The growth from a 48-hour agar slant suspended in 1 c.c. normal salt solution injected into the testis of rabbits produces an acute inflammatory condition which lasts for 7 to 10 days and then disappears without suppuration, the structure later appearing perfectly normal. On the other hand, animals similarly inoculated with staphylococcus and streptococcus die of peritonitis within 20 hours, while an injection of normal salt solution alone produces no reaction.

The following experiment was made on a medium-sized so-called white-faced ringtail monkey. On February 7, the animal, whose temperature was 100.8 F., was inoculated through the right Steno's duct with the culture from a 48-hour ascitic agar slant suspended in 1 c.c. normal salt solution.

February 8, temperature 103 F.; slight swelling of the parotid; refuses food.

February 9, temperature 103.2 F.; decided enlargement of the parotid; chews with difficulty, but does not appear sick.

February 10, temperature 101.8 F.; parotid about as it was yesterday; less difficulty in chewing; appetite good.

February 11, temperature 101.2 F.; parotid smaller than yesterday.

February 12, temperature 100.8 F.; swelling of parotid gradually disappearing.

February 13, temperature 100.2 F.; swelling of parotid gradually disappearing.

February 14, temperature 100.2 F.; parotid appears of normal size.

Most of my experiments have been on dogs. These animals seem to react in a characteristic manner to the introduction of the coccus into the parotid gland, while subcutaneous and intraperitoneal inoculations produce no results. Direct inoculation into the parotid gland of dogs causes a swelling of the gland, lasting for 7 to

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10 days. The injection of suspensions into Steno's duct produces in dogs a uniform swelling of the parotid gland which begins in from 48 to 72 hours, the gland continuing to enlarge for a few days, when it gradually returns to the normal size. In these animals the temperature during the period of the swelling of the gland ranges from 1 to 1.5 F. above normal; in no case did suppuration develop, and with the exception of difficulty in chewing for a day or two the animals appear to suffer no special inconvenience.

Injections into the duct of mixed cultures of the organism and staphylococcus causes edema of that side of the face and the parotid gland in 3 or 4 hours and abscesses form in 3 or 4 days. In two dogs that survived these injections after drainage of the abscesses the parotid gland was completely destroyed. One dog died on the fifth day of bacteriemia, another developed lung abscesses and died on the twenty-third day.

The following record of a single experimental inoculation of the diplococcus into Steno's duct in the dog illustrates well the changes thus produced in this animal:

February 24.—Small, young, black and white dog. Temperature, 102.5 F. Inoculated into the left Steno's duct with the bacteria from two 48 hours saliva agar slants suspended in 3 c.c. broth.

February 25.—Temperature, 102.5 F. No visible enlargement.

February 26.—Temperature, 103 F. Parotid enlarged. Dog whines when firm pressure is made over the gland.

February 27.—Temperature, 103.5 F. Parotid evenly enlarged and hard. Dog does not act ill, is playful and hungry, but experiences difficulty in chewing.

February 28.—Temperature 102.8 F. Gland about as it was yesterday. Pure cultures of the organism injected developed from aspirated fluid.

March 2.—Temperature 102.5 F. Swelling gradually disappearing.

March 5.—Temperature 102.5 F. Almost no enlargement of the gland.

March 6.—Temperature 102.5 F. Gland appears normal.

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Macroscopically, the enlarged parotid gland of inoculated dogs is of uniform firm consistence, the enlargement often reaching many times the size of the normal gland, and the cut surface is pinkish, exuding a slight amount of pinkish, rather turbid fluid. The neighboring lymph nodes are moderately swollen, but there are no gross changes in other parts of the body.

Microscopic examination of the parotid gland at the height of the enlargement shows a uniform infiltration of the tissue with plasma cells, small and large mononuclear cells, and polymorphonuclear leucocytes, the ducts being packed with cells. This infiltration begins in the interacinous tissue.

Examinations of the blood of the inoculated dogs shows a distinct leucocytosis, the increase being largely in the mononuclears.

Shortly after injection of the diplococcus into the parotid gland, the opsonic index of the serum of the injected animal begins to rise, reaching the highest point, about three, on about the fourth day, returning to normal gradually. So far as my observations go, a similar rise in the opsonic index with respect to the diplococcus occurs in human mumps, but many further observations are necessary before final statements may be permitted. Work along these and other lines, including the anatomic changes in the inoculated dog, is now in progress.

CONCLUSIONS.

From a case of mumps a diplococcus was isolated which corresponds in its essential characteristics to the organism obtained from mumps by Laveran and Catrin, Mecray and Walch, and the other investigators cited. Inoculations of suspensions of the diplococcus into Steno's duct in the monkey and in the dog produce an acute, uniform enlargement of the parotid gland accompanied with some slight fever. In the dog this en-

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largement is the result of an infiltration that consists largely of mononuclear cells, and is accompanied with a general increase in the mononuclear cells in the blood as well as a distinct rise in the opsonic index with respect to the diplococcus. Further studies, especially of the changes and reactions in human mumps, are necessary before it can be said whether or not this diplococcus is the specific cause of mumps.

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THE ALLEGED URINARY MANIFESTATIONS IN DISEASES OF THE PANCREAS.

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CINCINNATI.

It has long been an accepted fact that through experimental operations on the pancreas conditions may be produced that lead to certain changes in the urine. On the other hand, until 1904, when the work of Cammidge first appeared, there was not known in clinical medicine any alteration in the constituents of the urine, which was regarded as characteristic of, or as indicating, disease of the pancreas.

At that time Cammidge, of London, described in the Arris and Gale Lecture[1] his studies on the urine of patients suffering from pancreatic disease, and the reaction he then described has since become known as the "pancreatic reaction of Cammidge." As the direct result of criticism of his technic and conclusions, that author modified his procedure until he finally published his "improved" or "C" reaction, which is supposedly free from error.

THE WORK OF CAMMIDGE.

Briefly stated, the present contention of Cammidge is, that there occurs in the urine of patients having an inflammatory disease of the pancreas, a substance, which, on being boiled with strong hydrochloric acid,

1. Lancet, March 19, 1904; also the complete history of the test and its application, Robson and Cammidge: The Pancreas, Its Surgery and Pathology, 1907.

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will split off, or yield, a body that forms an insoluble compound with phenylhydrazin, after the method of preparing ozazones. With the exception of one case which he studied, Cammidge, in all his writings on the subject, has never attempted to define the nature of the body in question, or of the mother-substance. In the case referred to he determined the body to be pentose. On wholly insufficient evidence, or on no scientific evidence at all, Cammidge declares the crystals to be of a different substance in different diseases, and that their peculiar behavior to certain reagents may, within a minute or two, determine the particular disease from which the patient is suffering.

In an examination of 87 cases of disease of the pancreas, Cammidge found a positive reaction in 71, or in 82 per cent., and a negative reaction in 12. These 12 cases were out of 16 cases of cancer of the pancreas, all cases of acute and chronic pancreatitis having been positive. Of 117 cases of various conditions supposedly non-pancreatic 113 were negative in reaction and 4 positive. Of 50 specimens of normal urine all were negative. Cammidge, therefore, states[2] "The result of the improved or C reaction is an absolute one and is, therefore, independent of the personal bias of the investigator." And, again, "We maintain that a positive reaction is strongly suggestive of inflammatory disease of the pancreas, but we are not prepared to contend that it is pathognomonic of disease of the pancreas." Cammidge further states that the reaction disappears when the cause of the inflammation disappears.

CRITICISM OF CAMMIDGE'S WORK.

Whatever else is recorded in medical literature on this subject is relative to the work of Cammidge. It was unfortunate that the earlier reports by that author were lacking in that spirit of directness which is found in

2. Robson and Cammidge: The Pancreas, Its Surgery and Pathology, p. 250.

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his later work. Until Cammidge finally determined that the body, which he described in his improved or C reaction, was the substance to be looked for, he worked in the earlier, so-called A and B reactions, with glycuronic acid compounds admixed with the latter. The unscientific and ambiguous claims which he set forth, and his faulty technic called forth a spirit of antagonism in the critical mind. Those who repeated the early experiments of Cammidge unhesitatingly declared them to be wrong in principle and faulty in method,[3] and the subject was then ignored. The few clinical references as to the applicability of any other than the improved or C reaction are, therefore, without value.

With the appearance of this improved or C reaction a working basis was offered for further study. From a scientific standpoint by far the most important work was done by Felix Eichler[4] in the department of experimental biology of the University of Berlin. Eichler produced experimentally in two dogs a pancreatitis purulenta diffusa, and in one dog a pancreatitis hemorrhagica. Before the operation the urine of each dog was found to give a negative reaction. After the operation the urine in each case was found to give a positive reaction. Moreover, he determined the melting point of the crystals to be 182 C, which is not that of an ozazone of glucose, nor that of the compound of glycuronic acid. Beyond that he did not define the substance. It should be noted that Cammidge did not carry out this simple experiment, which should have been the fundamental study in the work, the importance of which he, above all others, conceived.

Eloesser[5] reported from the University Clinic at Heidelberg sixteen cases in which a positive pancreatic reac-

3. Ham and Cleland: Lancet, May 14, et seq., 1904; Schroeder: Amer. Med., September, 1904; Willcox: Lancet, July, 1904; Haldane: Edinburgh Med. Jour., November, 1905.

4. Berl. klin. Wchnschr., xliv, 1907.

5. Mitt. a. d. Grenzgeb. d. Med. u. Chir., xviii, 42, 169.

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tion was found in the urine, and in which the diagnosis was confirmed by operation. In one case the reaction was positive and there was no pancreatic involvement.

Edgecombe,[6] of London, reports a case of mumps in which the pancreatic reaction was positive. Cammidge himself made the test.

An interesting report is furthermore contained in the article of Watson.[7] Watson obtained a markedly positive reaction in all cases of chronic and acute pancreatitis, the diagnosis having been confirmed by operation, or postmortem; also in the course of other diseases, which were diagnosed as chronic pancreatitis because of the recurrence of suggestive clinical symptoms, such as epigastric pain and jaundice. A marked reaction was also found in a case of constipation, which improved by proper treatment, and he suggests that pressure of fecal masses on the pancreas may interfere with its function. In this case, and in several others, an alimentary glycosuria was noticed. Watson found, furthermore, a moderate or slight reaction in various other diseases, as of the heart, kidneys, liver, gall bladder, in colitis, gout, arteriosclerosis, alcoholism, and in two cases of exophthalmic goiter, one of which was benefited by the administration of pancreas emulsion, and in one the histologic examination showed round-celled infiltration of the pancreas. Positive reactions were also obtained in gastric ulcer and in malignant disease of the stomach. In many of these apparently non-pancreatic diseases an involvement of the pancreas, at least functional, can not be excluded.

Further contribution to our knowledge of urinary manifestations of pancreatic disease must be made from studies along definite lines. The experimental work of Eichler must be repeated. When the clinical diagnosis of pancreatitis is made it must be verified by operation during life or by necropsy. Lastly, clinical observations

6. Practitioner, February, 1908.
7 Brit Med. Jour., April 11, 1908.

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must be made in cases in which there are no pancreatic manifestations. The difficulties which are encountered in the effort to produce results that are entirely free from objection, considering the complexity of the material, need not be especially emphasized.

ORIGINAL INVESTIGATIONS.

The following observations, which I present as a small contribution to the subject, were made primarily with the object of investigating the occurrence of the pancreatic reaction in the urine in various conditions. During the past six months I have examined the urine from 85 individual cases. In all, 110 chemical analyses were made. Of the 85 patients 50 have been under my

RESULTS OF THE ANALYSES OF URINE FOR THE PANCREATIC REACTION.

Clinical Diagnosis.	Cases.	Positive.	Negative.
Chronic pancreatitis	4	3	1
Cancer of pancreas	1	1	
Cancer of stomach	3	2	1
Abscess of pancreas	1		1
Gallstones	4	1	3
Catarrhal jaundice	4	1	3
Tuberculosis of peritoneum	1	1	
Tumor of upper abdomen, probably of pancreas	2	2	
Cancer of liver	1		1
Cholecystitis	3		3
Tuberculosis pulmonalis	2		2
	26	11	15

personal care, having come under observation for various stomach and digestive disorders. Ten specimens were examined through the courtesy of other physicians, and twenty-five specimens were from patients in hospital wards, having no specific evidence of pancreatic disorders.

The remaining 59 cases included arteriosclerosis, myocarditis, angina pectoris, nephritis (uremia), cirrhosis of the liver, constipation, ulcer of the stomach (blood), achylia gastrica and nervous disturbances of the gastrointestinal tract. In all these cases the reaction was negative. Twenty-five of these were miscel-

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laneous hospital ward cases. Thus in the urine of sixty patients complaining of digestive disorders or having diseases of the digestive organs, the reaction was positive eleven times. In three of these eleven cases the clinical diagnosis of pancreatitis had been made. A few details of these cases may be of interest.

Cancer of the Pancreas.—The patient was under the observation of Dr. Forchheimer, who made the clinical diagnosis. The patient died shortly after that; no necropsy. The urine gave a more pronounced reaction than any other I have observed. I obtained enough of the crystals to determine the melting point, which was 180 C. So far as I know, this is the only clinical record of a melting point determined of this substance. In view of the fact that Eichler in his experiments on dogs found a body having a melting point of 182 C., it is likely that I obtained the identical substance.

Chronic Pancreatitis.—One patient was under the observation of Dr. Bettmann, suffering with violent, colicky abdominal pains, epigastric tenderness and recurring chills and fever. The reaction was well marked and subsided gradually with the patient's symptoms (six analyses). A specimen was immediately re-examined on the recurrence of fever in the course of recovery. The reaction was negative and the cause of the fever was found to be tonsillitis. In a second case, where the clinical diagnosis had been made by Dr. Forchheimer, the urine was examined after the patient had practically recovered. The reaction was negative. The two remaining patients were under my own observation, complaining of "intestinal indigestion"; the feces showed excess of fat and muscle fibers. (Reaction positive.)

Cancer of the Stomach.—In two cases a positive reaction was obtained. One case under my own observation developed an alimentary glycosuria. The diagnosis was confirmed by operation. There were dense adhesions so that the degree of involvement of the pancreas could not be determined. One case was under the observation of Dr. Bettmann. The operation also confirmed the diagnosis and found the pancreas involved. In a third case, which I was asked to see in consultation with Dr. Schulze, I made the clinical diagnosis of cancerous ulcer of the stomach. The pancreatic reaction was negative. The patient died within ten days, and I had the opportunity of making a postmortem examination. The clinical diagnosis was confirmed; the pancreas was found adherent, but the gland itself was not involved. There were no gallstones.

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Abscess of the Pancreas.—Under observation of and operation done by Dr. Whitacre. A specimen of urine three days after operation gave negative reaction.

Gallstones.—Of four cases operated on, one case, having a stone in the common duct, gave a positive reaction (case of Dr. Bettmann and Dr. Ransohoff); one case, with a stone in the common duct, gave a negative reaction; one case, having much post-operative pain, gradually subsiding, gave a negative reaction (case of Dr. Ransohoff); one case, gall bladder packed with stones, gave a negative reaction. The pancreas at the operation was found to be hard and nodular.

Catarrhal Jaundice.—Of four cases examined, one was positive and three were negative.

Tumor of the Upper Abdomen.—One case was from Dr. Holt's service at the Cincinnati Hospital. The tumor was regarded as possibly of pancreatic origin. The reaction was positive. No operation. The second case was under observation of Dr. Bettmann. Clinical features the same. The reaction was positive. The feces contained fat and muscle fiber.

Tuberculosis of the Peritoneum.—This case was under my observation for three weeks. The reaction was positive during a period marked by attacks of sharp pain (four examinations). Two months later the examination gave a negative result.

TECHNIC.

In these examinations the method as described by Cammidge has been strictly followed. His procedure consists in boiling the urine with strong hydrochloric acid, neutralizing the excess of acid with lead carbonate, removing the glycuronic acid and other interfering substances with tribasic lead acetate, and the excess of lead in solution with sodium sulphate, and the forming of the ozazone in the usual manner. This method does not permit of modification, except in one particular, which facilitates the work, namely, that one may work with smaller quantities after the initial boiling with acid.

The method that I have found convenient is as follows: 40 c.c. of the urine, filtered, acid reaction, free from albumin and sugar, are boiled with 2 c.c. of strong hydrochloric acid for ten minutes. After partly cooling, 8.0 gm. of lead carbonate are gradually added.

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When the reaction is complete, the mixture is chilled, filtered, and 10 c.c. of filtrate diluted to 20 c.c. with distilled water. This solution is precipitated with 2.0 gm. of tribasic lead acetate, filtered, and the excess of lead in solution removed by the addition of 2.0 gm. of sodium sulphate, bringing the mixture to a boil, chilling and filtering to 20 c.c. To this filtrate there is now added a mixture of phenylhydrazin hydrochlorate 0.80 gm., sodium acetate 2.0 gm. and of 50 per cent. glacial acetic acid 1 c.c., and the whole is boiled on a sand bath for ten minutes. The solution is then filtered while hot, and set aside to crystallize. The precipitation of crystals, sometimes only in microscopic quantities, of the characteristic formation of ozazones, makes a positive reaction.

The following precautions must be observed:

1. The urine must not contain albumin or sugar, and must be fresh and filtered clear.

2. Positive reactions must be verified by making the phenylhydrazin test for free sugar in the urine, using the same method without previous boiling. Fehling's test is not sufficiently delicate. The sufficiency of removing sugar by previous fermentation has not been proved.

3. Tribasic lead acetate ($Pb(C_2H_3O_2)_2.2PbO$) must be employed. The solution of lead subacetate of the U. S. Pharmacopeia is not satisfactory. I have employed it side by side with the tribasic lead acetate and have obtained misleading results with the former. Before realizing this difference I had some correspondence with Cammidge on the subject, and I agree with him that the tribasic lead is the only suitable precipitant, because of the uncertain and indefinite composition of the pharmacopeial preparation. The positive reaction may be marked or may require microscopic examination. I have noted precipitates that were not crystalline and, therefore, negative. Precipitation may take place immediately on filtering or may occur after standing

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twenty-four hours. Except as to size, the crystals that I have observed in various positive reactions were apparently of the same system. I can not concede any value whatever to such tests as solubility in sulphuric acid, as tending to point to the nature of the disease, and I have, therefore, never applied this test.

PATHOLOGY.

The apparent value of the pancreatic reaction in the urine makes it reasonable and of interest to reflect on the nature of the conditions that may give rise to this manifestation. The proven results so far obtained would suggest, first, that inflammatory conditions in the pancreas give rise to the reaction. Second, we may infer that chronic pancreatitis *per se* does not give rise to the condition, because the reaction disappears when the cause, such as gallstones in the common duct, has been removed, the infiltration of the gland, the mark of the chronic inflammation, remaining. The reaction, therefore, can not be said to be the direct result of the chronic pancreatitis, but rather of a functional disturbance coincident with the existence of causative factors. Third, it has been shown that pancreatic tissue contains a larger amount of pentose yielding material than any other tissue in the body. Therefore, disintegration, as in cancer and abscess, may lead to absorption and subsequent excretion of pentose. Fourth, pancreatic disturbance may lead to incomplete combustion and excretion of substances of the nature of aldehydes and ketones. Fifth, in the presence of fat necrosis, glycerin products, incompletely oxidized, may give the reaction. Sixth, impaired pancreatic digestion in the intestines may lead to absorption of certain substances that give the reaction.

Cammidge himself suggests that in the absence of pancreatitis, conditions accompanied by rapid tissue changes may produce substances giving the test.

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CONCLUSIONS.

The conclusions that may be drawn at this stage of the investigation are limited. They are as follows:

1. It has been proved that inflammatory and destructive disease of the pancreas may give rise to the appearance of certain, as yet undefined, bodies in the urine, belonging possibly to the sugars or related compounds.

2. The reaction is not pathognomonic for disease of the pancreas, in the clinical sense.

Extensive clinical observations on the urine in pancreatic and other diseases must finally determine the value of the pancreatic reaction.

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FURTHER RESULTS IN SUPRARENAL TRANSPLANTATION.*

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In a former communication[1] one of us reported a series of thirty-two cases in which suprarenal transplantation had been attempted. In this first series, a part of the animal's suprarenal was transplanted to its own kidney. At least one positive functional survival of such a graft was obtained. Partial proof of functionating suprarenal grafts was obtained in several other instances. The indication of successful transplantation, consists in survival of the animal, in the absence of all suprarenal tissue, other than that of the graft, and in the histologic demonstration of a living graft containing medullary cells.

In the present series of thirty cases, transplantations have been made into the thyroids, testes and kidneys of dogs and rabbits, not only in the same animal, but also from one animal to another of the same species. The results of implantation into the testes and thyroids were all negative. Positive results were obtained only in those cases where the kidney was used as the receiving tissue.

DETAILS OF TECHNIC.

The complete experiment of transplantation into the kidney, whether the giving and receiving animal are the same, or the receiving animal is another of the same species, consists of three stages, as follows:

*From the Physiological Laboratory, University of Buffalo.
1. Am. Jour. Physiol., 1906, xv, No. 5.

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First stage.—One suprarenal gland is removed in its entirety. A sagittal third of this, or of a gland from another animal, is introduced into an opening in the lower pole of the kidney cortex, patterned as nearly as possible after the graft to be implanted. The graft is held in place by means of two or more silk sutures passed over it and through the kidney capsule and cortex, on either side. As a rule, the surface of the graft is brought flush with the kidney surface. By cutting off a thin slice from the lower portion of the graft and from each pole, five raw surfaces are brought into apposition with the fresh surfaces of the kidney wound. Care is taken to prevent the intervention of blood-clot between the surfaces of the graft and the kidney. The kidney is then allowed to drop back into its bed, and the external wound is closed.

Second stage.—A varying period after the first operation, the animal's remaining suprarenal is completely removed. In the absence of accessories or remnants, which may have been overlooked during the first operation, there should be no suprarenal tissue remaining, other than that of the graft. If such is the case and the graft has undergone necrosis, the animal should die of suprarenal insufficiency, unless death occurs earlier through anesthesia, hemorrhage, or shock.

Third stage.—If the animal has survived the second operation for a considerable period, the kidney containing the graft is removed. If other causes of death, such as shock and renal insufficiency can be excluded and death occurs within three or four days, preceded by marked muscular weakness and tremor on exertion, it is probable that the cause of death is suprarenal insufficiency, and that the graft had been functionating. The proof is completed by failing to find suprarenal tissue at autopsy and by the histologic demonstration of an apparently living graft containing remnants of medulla. Additional proof would be the demonstration of blood pressure raising properties of graft extracts.

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PROOF OF FUNCTIONING.

Complete proof of functionating graft survival, as outlined above, we have obtained in two cases. In one of these the rabbit's suprarenal was transplanted into its own kidney. Thirty-six days later, the remaining adrenal was removed, and seventy-seven days after the second operation, the kidney containing the graft was removed. The rabbit recovered rapidly from the immediate effects of the operation and seemed quite normal for the first day. The morning of the second day, the animal appeared apathetic; did not move unless disturbed, but showed no pronounced muscular weakness; did not eat. In the afternoon muscular weakness was more pronounced, and there was slight tremor on exertion. When not disturbed there was still slight tremor of the hind quarters and a gentle swaying motion; dullness and apathy were increased. It was found dead, the following morning, stretched out on side, head thrown back. At autopsy the viscera appeared normal. There was no evidence of peritonitis and no suprarenal accessories or stump could be found.

The left kidney, containing the graft, which was removed at the third operation, was adherent to the omentum over the surface of the graft. These omental adhesions were very vascular. After separation of the adhesions, the graft itself was not distinguishable on the surface, but showed on cross section through the kidney as a dark hyperemic mass with a central yellowish core, about two millimeters in diameter and five millimeters in length. Microscopic examination of the graft, which had been fixed in Zenker's fluid, showed this as an oval mass at the bottom of the kidney wound and consisting of cells which stained well with hematoxylin and eosin. Outside of these and extending toward the external surface there was a mass without definite cellular structure, containing many areas of extravasated blood and occasional islands of what appeared to be cells of the suprarenal cortex. The central

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cells, as well as several small islands separated from the main mass by new formed connective tissue, appeared to be of the suprarenal medulla type. These latter cells also gave a reaction with chrome salts.

The second case (sixty), in which the three stages were completed, consisted in the transplantation of the suprarenal of one rabbit into the kidney of another. The rabbit's remaining suprarenal was removed thirty-six days after the introduction of the graft. The animal made an uneventful recovery. Twenty-nine days later, the kidney, containing the graft, was removed. Death occurred forty-three hours after the third operation, preceded by symptoms similar to those recorded for the first case.

At autopsy no abnormality was found in any of the viscera and there was no evidence of peritonitis. The abdominal vessels were unusually distended, which was likewise the case in the first experiment reported. No accessory adrenals or adrenal stumps were found. The kidney, which contained the graft, was found, at the time of the last operation, to be rather firmly adherent to the left lobe of the liver. The graft was visible at the kidney surface as a yellowish body, about two millimeters wide and four millimeters long; the portion imbedded was about two millimeters in its greatest diameter.

Microscopic examination showed the graft as a wedged-shaped mass of cells walled off from the kidney by new-formed connective tissue, but with very little, if any, inflammatory reaction in the adjoining kidney tissue. The cells of the wedge were large in size and spherical to polyhedral in shape, with relatively small nuclei and much cytoplasm. The nuclei stained well with hematoxylin, and the cytoplasm faintly with eosin. It is difficult to identify them with the cells of the normal gland, but from the fact of their reaction to chrome salts and their size and arrangement it seems probable that they are of the medullary type.

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Four rabbits survived the third operation—the removal of the kidney containing the graft. These were killed later, and found to possess accessory suprarenals. In two of these cases, living grafts, containing medullary cells, were found. In the third, the graft was partly necrotic and no medullary cells could be demonstrated. In the fourth, there was hydronephrosis and a partly necrotic graft.

One rabbit met with an accidental death through anesthesia, at the third operation, ninety-four days after the introduction of the graft and fifty-one days after the removal of the other suprarenal. At autopsy, no remaining adrenal stump or accessory bodies could be found. The graft itself was living and contained cells of medullary type. In this case, the transplanted suprarenal was obtained from another rabbit.

Another rabbit died through accident at the second operation, thirty-four days after the introduction of the graft. The graft, although partly necrotic, contained some islands of medullary cells.

In still another rabbit death occurred eighteen days after the removal of the second suprarenal. At autopsy no accessories were found, and the graft was necrotic. In this case the graft must have been still functionating at the time of the second operation, the process of necrosis having been completed eighteen days later, at which time the animal died from suprarenal insufficiency.

The best histologic picture of a graft is shown in an animal which died from some undetermined cause, eight days after the primary operation. In this case the cross section of the graft looks like a section through normal suprarenal, distinctly showing all the zones.

Of the remaining cases of this series, some animals died through accident at the primary operation, and the others from suprarenal insufficiency after the second operation.

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SUMMARY.

Including the cases of our first report with those recorded here, we believe that satisfactory evidence of functioning suprarenal graft survival has been given in, at least, three cases. One of these consisted in a transplantation from one animal to another. In several other instances where complete proof could not be obtained, there is a strong probability that grafts were functionating. So far as we know these are the first successful cases of suprarenal transplantation with preservation of function.[2] That the original sympathetic nerve connections of the gland may be severed without apparent disturbance of function has been shown by the successful cases of transplantation.

The kidney seems to be the best structure for the reception of the grafts. The method of removal of the kidney, with the graft, in the third stage of our experiment, has, we believe, in no instance, been a disturbing factor, since those animals which had accessories survived, with apparently no ill effect, the removal of one kidney.

Whether the graft alone, in any of these cases, would have been sufficient to carry on the suprarenal functions indefinitely, we can not say. The longest period of graft survival which we have recorded is 247 days.

With improved technic and more uniform success in animal experiments, it does not seem unreasonable to attempt suprarenal transplantation as a therapeutic measure in Addison's disease.

In conclusion we wish to thank Dr. James A. King and Dr. W. Ward Plummer for valuable assistance in some of the earlier operations.

2. Note made on reading proof: Since the reading of this paper, there has come to our notice a report (Haberer; Arch. f. Klin. Chir., lxviii, No. 2, 1908), of suprarenal transplantation into the kidneys of dogs and rabbits. In these experiments, however, a portion of the original blood supply was left undisturbed, and there was continuity of tissue between the intra and extra-renal portion of the gland. No adequate evidence of functional graft survival was given.

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DISCUSSION.

DR. W. M. L. COPLIN, Philadelphia: An interesting fact in regard to implantation is the suggestion, which has been accentuated by Dr. Busch's admirable communication, that transplantation in the presence of an adequate, normal suprarenal body, or where suprarenal secretion is sufficient, is followed by hyperplasia of the transplanted suprarenal. A very interesting and highly suggestive phase of this work was brought out two years ago by French workers, during attempts to induce hypernephromata by transplantation of the suprarenals. Some times the graft takes and a tumor results; in other instances no neoplasm is produced, although the transplanted tissue survives; of course, in most cases the graft dies, autolyzes and disappears. When the graft remains and its cells proliferate without evidence of suprarenal intoxication, we at once think of Professor Adami's suggestion that when cells are no longer required to maintain their secretory functions they revert to a more highly manifest hyperplastic and productive activity.

DR. H. G. WELLS, Chicago: In 1900 I performed a small series of experiments with the object of transplanting the suprarenal into the kidney in young guinea-pigs, with the object of seeing if from such misplaced adrenal tissue a hypernephroma might develop, but the results were negative. I never got any tumor formation, and only occasionally evidence of survival of adrenal cells. The results were so negative that they were never published.

DR. A. J. CARLSON, Chicago: Is there any explanation for the fact that the graft takes only in the kidney? Why should it not take in other tissues in the vascular supply?

DR. W. B. CANNON, Boston: Have grafts been placed in the spleen and other organs? Why not make use of the spleen also in these cases?

DR. F. C. BUSCH, Buffalo: The point brought up in regard to hyperplasia is interesting, but one on which I am not competent to speak. In these animals, at the first operation, only one adrenal was removed, a part of this or a similar portion of the gland from another animal, being used for transplantation. The remaining adrenal was sufficient to carry on the function until the second operation, even if the graft was inactive. I have not seen any instance of overgrowth or new growth on the part of the transplanted cells.

It is interesting to note that in those animals in which the graft became necrotic, death occurred soon after the removal of the remaining suprarenal, eight to fourteen hours after the second operation. This was due, I believe, to suprarenal insufficiency, and not to the operative procedure alone. In those subjects surviving the removal of all other adrenal tissue, we have nothing but the graft to account for such survival. After

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the removal of the graft itself, at the third operation, death occurred later, within two to four days, with progressive symptoms of suprarenal insufficiency. It would seem that there had been some adaptation of the animal to the small amount of functionating suprarenal of the graft.

The questions of Dr. Carlson and Dr. Cannon as to the reason for success of transplantation into the kidney and failure in other organs, I can not answer definitely. We did not attempt transplantation into the spleen, partly because, in the rabbit, the spleen is much too small for the purpose. The kidney was chosen because of its ease of access, its vicinity to the suprarenal, its vascularity, ease of handling and control of hemorrhage, and because of its close developmental relations to the suprarenal. I have no explanation of the failure of transplantation into thyroids and testes. Survival of suprarenal cortex after transplantation into the testis has been recorded.

The difficulties involved in the three stages of the experiment I have not specifically mentioned. One of these has been the close relation between the adrenal and the vena cava or renal vein, or both. In attempting complete removal of the gland there is great danger of fatal hemorrhage from wounding these veins.

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THE NATURE AND THE CAUSE OF EDEMA.*

MARTIN H. FISCHER, M.D.
OAKLAND, CAL.

INTRODUCTION.

The remarks that follow represent one of the possible applications of a principle which for some time past I have been interested in establishing experimentally, namely, that in the variable affinity of colloids for water we have the explanation of many of those physiologic phenomena which are characterized by a storage or a migration of water.[1]

If we ignore certain "vitalistic" conceptions of edema in which fantastic properties of "living" cells are supposed to account for the phenomena observed, the increased amount of water held by tissues in a state of edema is usually attributed to "changes in blood pressure," and to "alterations in the permeability of vessel walls." The alterations in the permeability of vessel walls have never been demonstrated experimentally, and all efforts to produce states of edema through simple increase in blood pressure have failed. The slight edema observed by some investigators after prolonged intravenous injections at high pressure of enormous amounts of various liquids can be explained more easily by changes brought about in the colloids than through simple pressure effects.

Here and there one meets a phrase in the discussion of edema which suggests that the author at least assumes

*From the Laboratory of the Livermore Sanatorium, Livermore, Cal.

1. Fischer, M. H.: Physiology of Alimentation, New York, 1907, pp. 268, 182-187, and 267-269. Fischer, M. H., and Moore, Gertrude. Am. Jour. Physiol., 1907, xx, 330.

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the possibility of a cause for this condition in the tissues themselves, but I know of no experiments planned to actually prove this point, or of any attempts to define the nature of these tissue changes physico-chemically, except those of Jacques Loeb,[2] who, ten years ago, tried to find in an increase in the osmotic pressure of the tissues the cause of the increased absorption of water. The inadequacy of this explanation has since become apparent, but the experimental facts adduced by this author to show that the cause of edema resides essentially in the tissues are of permanent value, and should have received a recognition at the hands of pathologists which has never been accorded them.

THE CAUSE OF EDEMA RESIDES IN THE TISSUES.

For a starting point in our discussion it is well to take the results of some experiments which prove conclusively that the cause of edema resides primarily in the tissues. When this is proved we can say that tissues become edematous not because water is forced into them, but because they absorb water from liquids flowing through or about them. An analysis of the changes in the tissues leading to the increased absorption of water may then be attempted.

My experiments consisted in passing a ligature about one hind leg of a frog or a toad sufficiently tightly to close both the veins and the arteries of that leg, and then placing the animal in a vessel containing enough water to cover the legs. A ligature placed just above the knee where lack of musculature makes ligation of the vessels an easy matter proved most satisfactory. In such an entire absence of the circulation the ligated leg begins to swell and in the course of a few days develops an intense edema. The edema is well marked at the end of twenty-four hours, and in two or three days

2. Pflüger's Archiv. für die gesammte Physiologie, 1898, lxxi, 468.

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the weight of the ligated leg may come to be almost twice that of the unligated leg.

The picture presented by the edematous legs is a duplicate in every way of the most intense states of edema observed clinically. The tissues are boggy, pit on pressure, and when incised allow the escape of fluid. If the ligature is left in place for two to three days small vesicles form which may enlarge into great blebs containing a blood-stained serum.[3] Later, these blisters rupture and allow the escape of their contents, and the weight of the ligated leg diminishes. This progressive diminution in weight continues due, in part, to loss of substance, in part to changes which no longer allow the leg to hold the large amount of water it once held,[4] until finally the ligated leg weighs no more than the unligated. If the animal is kept sufficiently long (two to three weeks) the ligated leg is lost entirely (gangrene).

The increase in the weight of the ligated leg is entirely due to the absorption of water. This water is held in the skin, in the tissues composing the body of the leg—chiefly the muscles—and in the lymph spaces found between the skin and the underlying tissues. With this third division must be mentioned the fluid found in the blisters, which it is well to point out, in passing, are formed in the body of the skin.

As is to be expected, the development of an edema in the ligated leg of a frog or a toad kept in a little water will occur when the animal has been pithed just as well as in the normal animal, but if the frog or toad is killed, the difference in the weight of the two legs does not appear. This is not, however, because the edema does

3. A circulatory system and the pressure of circulating liquids have therefore, nothing to do with the formation of blisters. The necessary elements for the formation of such pathological structures reside entirely in the tissues themselves.

4. The tissues of the leg undergo autolysis. In consequence colloids having a great affinity for water are changed into such as have a lesser affinity, or they may be reduced even to crystalloids.

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not develop in the ligated leg, but because it develops equally well in the other leg (which has through the death of the animal been deprived of its circulation). Herein is found the explanation of the fact that the tissues of dead bodies which are kept in water swell.

An objection which is likely to be lodged against my experiments is that I did not tie the ligatures sufficiently tightly to shut off both veins and arteries. That this was accomplished is proved by the fact that if the frog or toad was kept in a dry vessel the ligated leg soon dried so as to become brittle, while the unligated leg remained moist.

CHARACTER OF THE TISSUE CHANGES IN EDEMA.

It is clearly shown by these simple experiments that the severest grades of edema may exist without the presence of any "blood pressure" or a demonstrated "increased permeability of blood vessel walls." I shall try to show now that edema represents nothing but an increased affinity of the tissue colloids for water. Such an increased affinity of the colloids may be brought about in either or both of the following ways: *First,* in conditions leading to edema, various substances (particularly acids) capable of greatly increasing the affinity of colloids for water are not removed as they should be or are produced in abnormal amounts, and *second,* colloids having but little affinity for water are changed into such as have a greater affinity.

The first of these two factors plays the predominant rôle and is the only one discussed in this paper. We may regard it as settled that the amount of water held by a tissue under normal circumstances is essentially a function of its colloidal constitution for the same external circumstances which make certain so-called hydrophilic colloids either take up or give off water, make animal tissues do the same.[5]

5. Fischer, M. H., and Moore, Gertrude: Am. Jour. Physiol., 1907, xx, 330.

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If, now, the conception of edema as a condition in which this affinity of the tissue colloids for water has been abnormally increased is correct, it must be possible to prove three things: (1) That protoplasm is colloidal in constitution. (2) That in the variable affinity of colloids for water we have a force of sufficient magnitude to account without strain for the maximum amount of water ever found absorbed by tissues in a state of edema. (3) That conditions leading to an increased affinity of their colloids for water exist in the tissues under circumstances associated with the development of an edema. We shall briefly consider each one of these.

1. Since the classical researches of Hofmeister, Pauli, Hardy and a few others, it is no longer questioned by any one that protoplasm represents a colloidal solution in which may be found embedded or dissolved a greater or smaller amount of extraneous material that need not be directly connected with the vital activities of the cell. Since colloids may, however, exist in several states, it is well to decide in which they are present in the cells. For our purposes it is best to distinguish between such colloids as have the power of swelling when placed in water (the so-called hydrophilic colloids) and such which do not possess this property. Many reasons can be adduced to show that protoplasm represents essentially a mixture of several hydrophilic colloids. Not only do dried albumin, fibrin, gelatin, etc., swell when placed in water, but a direct analogy can be proved to exist between the swelling of muscle, for example, and fibrin. The same conditions which make fibrin either take up or lose water, make frog muscle do the same.[5]

2. It must now be shown that in the affinity of colloids for water we have a force of sufficient magnitude to account without strain for the maximum amount of water ever found to be absorbed by tissues in a state of edema. This can be done very easily. The severest edemas found in frogs no more than double the weight

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of the normal leg. Some observations made on patients indicate that the severest states of human edema give values which lie far below this.

We will now, for the sake of argument, neglect the inorganic constituents of the tissues, and say that three-fourths of the body represents water, and only one-fourth various organic substances. These organic substances belong almost all of them in the group of the colloids. On the basis of the figures which I have just given, 1 gram of dry body substance would therefore equal 4 grams of moist body substance, and this in a state of edema may absorb enough water to double in weight, that is weigh 8 grams. In terms of the dry weight of the body, the colloids are therefore required to absorb in a state of edema, seven times their weight of water. It will be sufficient evidence to show how easily colloids accomplish such an absorption of water when I use as an illustration the amount of water that fibrin will absorb under appropriate circumstances. In a weak solution of acid or alkali, dry fibrin may absorb from 20 to 40 times its weight of water.

3. Lastly, it must be proved that in conditions leading to edema substances are formed which are capable of increasing what we may call the normal affinity of the tissue colloids for water. Various substances are capable of markedly influencing the amount of water held by a hydrophilic colloid.

With the exception of alkalies, we find that acids, including carbon dioxid, are the most powerful substances thus far known for increasing the affinity of colloids for water, and it is in either the retention or the abnormal production of acids in the tissues as rendered possible in conditions leading to an edema, that I see the chief cause for its development. To illustrate how powerfully a little acid modifies the amount of water absorbed by a colloid, we need only recall the fact that while fibrin will scarcely swell sufficiently in distilled water to double

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its weight, it will hold twenty times its weight of water if a little acid is added.

The production of acids in conditions leading to edema has been shown repeatedly. In the described experiments in which one leg of a toad or a frog is ligated, the acid reaction of the tissues may be sufficiently pronounced to evidence itself with the use of any of the common indicators. In some analyses of various edema fluids made in Prof. Friedrich Müller's clinic in Munich I found that these always showed an acid reaction toward phenolphthalein, even after the carbon dioxid contained in them had very largely been allowed to escape. We know, moreover, from Hoppe-Seyler's analyses that edema fluids contain various acids—lactic, valerianic, succinic, butyric—from Strassburg and Ewald's accounts that their carbon dioxid tension is far above that of ordinary venous blood and from Araki's studies that in conditions associated with a lack of oxygen—just such a state as is produced through circulatory disturbances—organic acids are produced in excessive amounts. Ranke's observation that a muscle after exercise absorbs more water than a resting one, coupled with the fact that acids are produced during muscular activity, also finds a ready explanation through changes brought about in the state of the colloids and lends support to the ideas advanced here.

CONCLUDING REMARKS.

It may not be amiss, in conclusion, to point out a number of facts which in a sense are corollaries of what has been said. Attention has already been called to the fact that dead bodies kept in water become edematous. This is due to the fact that after death the tissues become acid, and absorb water from their surrounding medium. For the same reason gangrenous tissues swell if a source of water is furnished them either from without or through the blood and lymph vessels. In gangrene due to occlusion of a vein it is well-known that

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the tissues are ordinarily moist and swollen, while a gangrene due to occlusion of an artery is ordinarily dry.

The conception of edema offered here holds for local as well as generalized edemas. In fact, one form of local edema furnishes what amounts to experimental proof of the ideas advanced. Reference is made to the rapidly developing edema which follows the stings or bites of various animals capable of carrying formic or other acids into the wound produced by them. Formic acid is exceedingly active in increasing the affinity of various colloids for water. This explains why its introduction into the tissues—as through a flea bite—is followed by such a rapidly developing local edema. That circulatory disturbances are not primarily responsible in this case is indicated very clearly by the fact that the edematous tissues are initially white and only after resolution has commenced does an increased flow of blood occur through them. "Flea bites" can, in fact, be perfectly mimicked with a needle, a little formic acid and a hydrophilic colloid. If a gelatin plate is pricked with a needle dipped into formic acid, and a little water poured over the gelatin plate, wheals soon develop on the surface of the gelatin, which, in shape and in the rate of development, are identical with those which follow the bite of a flea or the prick of a formic-acid-laden needle in the skin of a human being.

As another form of local edema which finds a ready explanation on the basis of the ideas advanced here, we may mention glaucoma, and the imbibition of water by the crystalline lens. Even if we do not accept the view that no circulation whatsoever occurs through the vitreous and aqueous humors, we must at least admit that a well defined circulation as maintained through blood and lymph vessels is difficult to demonstrate experimentally. Workers on the eye have therefore been unable to find the explanation of glaucoma in any disturbances in the pressure, *per se,* of circulating fluids;

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and no attempt has ever been made to account for the absorption of water by the crystalline lens, for here the absence of a circulation is only too apparent. The facts observed are, however, easily explained when it is remembered that the humors of the eye and the crystalline lens represent typical colloidal bodies and that not alone the production of the slightest amount of acid or an accumulation of carbon dioxid, even a mere decrease in the absolute or a slight shifting of the relative concentrations of the various salts found in these substances is followed by so great an absorption of water that the severest grades of clinical glaucoma are easily accounted for.

I wish, finally, to say a word regarding the active or passive migration (diapedesis) of the formed elements of the circulating fluids into the tissues. My reason for bringing up this point at this time is because in the later stages of edema the red blood corpuscles frequently pass over into the tissues, and I would like to protest against the present generally accepted belief that the red blood corpuscles, for instance, pass out of the blood vessels through so-called stomata. Such an idea, is, on its very surface, gross, if not absurd, for how can such holes exist in the blood vessel walls? The histologic evidence of their existence is entirely inconclusive. I would like to call attention to a property of colloids which allows a ready explanation, not only of the passive passage of such formed elements as the red blood corpuscles through the walls of the blood vessels, but also the active movements of the ameboid cells. It is perfectly possible for one colloid to pass through another without losing its identity or leaving any mark behind indicative of its passage. The passage of a liquid body through a colloid can be very nicely illustrated by the movement of a mercury drop through a solidified gelatine of the proper concentration. Under the influence of gravity a mercury drop will move anywhere

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through a gelatin mass, in which, of course, there are no stomata, and leave no evidence of its passage behind. Similarly red blood corpuscles can, under the influence of a pressure not exceeding that in the blood vessels, be blown into a stiffened gelatin. Here one colloidal body moves through another. Whether one such body will pass through the other is simply a matter of relative surface tensions. Under ordinary circumstances this relation is not such in the body as to allow the red or white blood corpuscles to pass into the tissues (we might say be swallowed), but in lack of oxygen, under the influence of chemical agents (chemotaxis), etc., the proper ratio may be produced.

For the same reason that red and white corpuscles are capable of passing into and through the tissues, bacteria may be taken up by either fixed or motile cells. Pathologists have often wondered how a bacterium may enter the tissues at one point, and leave behind no evidence of entrance. This is because one colloid body may pass through another; from the alimentary tract, for instance, into the walls of the intestine and through this into one of the circulatory systems, and again out of these through the substance of the kidney into the urine.

In this way an infectious agent may wander through any of the tissues of the body, provided the proper surface tension relationships are present, without leaving behind any mark indicative of its passage. Through discussion of the opsonins special interest has recently been attached to the methods by which the surface tension relationships of bacteria to fixed or motile cells may be altered under physiologic and pathologic conditions. An opsonin is nothing but a substance to which has been given an evanescent name, which is capable of so altering the relationship of surface tension of bacterium to cell as to allow the former to be taken up. Many conditions are capable of markedly changing

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surface tension relationships, and there can be no doubt that we shall on some day not far distant become acquainted with innumerable simple chemical bodies which will, when added to mixtures of leucocytes and bacteria act as our now mysterious "opsonins." We must, however, carefully distinguish between the mere inclusion of an infectious agent and its destruction. Many workers on the opsonins take the swallowing of a bacterium by a cell and its destruction to be synonymous. This is a grave mistake and can not be too vigorously guarded against. Inclusion and destruction are two separate processes, and their mechanism must be separately considered.

DISCUSSION.

DR. A. J. CARLSON, Chicago: I am not familiar with the pathologic side of edema as such. Of course, when one ligates a frog's leg, as Dr. Fischer has done, one produces very abnormal conditions. As far as I know, in the case of local edema at least, there is no evidence of the formation of this specific substance. I think, however, that there is something in this suggestion, but it is only one of the factors in the tissue cell. I do not know that we can throw away the conception of such terms as secretion, inasmuch as terms like that stand for a mass of material the nature of which we do not understand. Nobody, of course, pretends to say that such terms are positive. I think that perhaps two more factors must be considered in edema, namely, the lymphatics and also the blood vessels.

DR. A. D. HIRSCHFELDER, Baltimore: The conditions of edema in which the limb is ligated and both circulation and lymph flow are cut off are to be differentiated sharply from those in which there is some residual circulation. In the former case, as shown by Loeb ten years ago, differences of osmotic pressure are possible, and probably actually occur. I am under the impression that Loeb did demonstrate some difference between the osmotic pressure of the tissues of the frog's legs above the ligatures as compared with the parts below them. In the latter case the circulation is always rapid enough to allow osmotic interchanges to go on, and marked differences in osmotic pressure do not take place. I therefore think that this is the difference between the two forms of experimental dropsy. The injection of formic acid and other substances certainly brings about injury of the endothelial walls of the capillaries quite as much as it does the very interesting phenomenon of absorption by colloids.

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DR. W. H. WELCH, Baltimore: Are the phenomena Dr. Fischer finds applicable to all forms of edema? It can hardly be that a single explanation can apply to all varieties of edema, the mechanical as well as the cachectic. We shall probably not have a clear understanding of edema, of the events, for example, which intervene between the occurrence of passive hyperemia and the accumulation of fluid in the tissues, before the physiologists have settled many disputed matters connected with the production and absorption of lymph. There are certain striking peculiarities of pulmonary edema which must be taken into account on any hypothesis framed to explain this variety. As is well known, general pulmonary edema can appear very suddenly and can disappear with equal rapidity. Can the factors which Dr. Fischer believes to be operative explain these features of pulmonary edema?

DR. H. G. WELLS, Chicago: One thing which Professor Welch just said has always troubled me in applying most of the questions in relation to edema forms; that is the formation of pulmonary edema, particularly the alveolar form in which edema occurs where there are practically no cells and where there is nothing to cause fluid to run. Why should there be an accumulation of fluid in the alveolar space where there are no cells to attract the fluids? To provoke the alveolar fluid? But there is too little of it to account for the rapid production of edema.

DR. W. B. CANNON, Boston: Dr. Fischer stated that gelatin was capable of taking up fifteen to twenty times its weight of water. As I understand it, that is the dry weight. I should like to know whether the initial amount of water normally associated with the colloids would still allow enough more to be taken to account for the results we see.

DR. MARTIN H. FISCHER, Livermore, Cal.: It seems to me that when marked edema can be produced, as it is certainly produced in these frogs, it is going out of the way to hunt trouble to insist that the lymphatic circulation must play a rôle. The burden of proof rests on this side of the argument. I am much more inclined to believe that the lymphatic circulation is the consequence of tissue activity than that it causes tissue activity. There is no circulation in these ligated frog's legs and the edema has to be explained without a circulation.

So far as the physiologic functions of the endothelium are concerned we may, of course, if we wish, use the word "secretion," but the word is not an explanation. I believe that we are going to find the explanation of the secretion of fluid into the alveoli of the lungs and into tissue spaces generally in changes in the colloids of the surrounding tissues. These after having become edematous seem to suffer a secondary change, an autolysis perhaps, through which their affinity for water is decreased, and they drop a part of their water, as it

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were "secrete" it into the alveoli or tissue spaces. I do not care to discuss this point further because I am experimenting on it.

To illustrate my remarks to-day, I spoke only of such colloids as can absorb water and maintain their shape. This was done to prove that colloids have an intense affinity for water independently of any osmotic conceptions. As a matter of fact the lymph and different body fluids often have enormous amounts of colloids suspended in them, and these particles in such pseudosolution also have an immense affinity for water, which I have not at all considered in my paper.

I consider it quite immaterial whether an edema is produced slowly or rapidly—whether the circulation is shut off in a moment by tying a string around the leg, or the leg is deprived of oxygen more slowly, the condition affecting only the rate of development of the edema and having nothing to do with its essential cause.

The question whether the ideas advanced are applicable to all forms of edema is one that must be tested and answered by the future. My answer now is "yes." There are a large number of edemas. The simplest forms develop in consequence of heart lesions, thrombosis, and things of that sort. When edemas similar in nature to these are produced in frogs the acid formed is so high that it shows itself readily when litmus paper is touched to the muscles. The edemas of nephritis, for instance, I explain by saying that poisonous substances are produced or retained in this condition which act on the tissues of the body and so alter their metabolism that substances capable of increasing the affinity of the colloids for water, such as acids, are produced. These acids would then influence the colloids of the tissues. Various irritant oils when painted on the skin will produce an inflammatory edema, but these oils when applied directly to such colloids as gelatin or egg albumin, do not increase the affinity of these substances for water. We know, however, that there are a number of poisons which produce changes in the tissue that are entirely analogous to those produced through direct lack of oxygen. Potassium cyanid when present in a tissue produces all the changes characteristic of lack of oxygen—the production of acids and the swelling and bursting of the cells affected. But the details of how edema is produced by such indirect means has to be worked out.

All my remarks had to be more or less dogmatic. I do not believe that my ideas must necessarily account for everything in the pathology of edema. Just now it looks to me as though changes in the colloids would explain 97 per cent. of it. Osmotic ideas seem to account for less than 3 per cent. Some day probably with new conceptions in physical chemistry, my own 97 per cent. will be reduced to 40, 30 or 20 per cent.

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A question raised was that of the rate of development of edema. I consider it one of the best arguments in favor of the views advanced that colloids are capable of changing their affinity for water in the short periods of time sometimes allowed tissues to develop an edema. In five minutes fibrin will readily take up or give off an immense amount of water. Were I to add a little calcium chlorid to a tube filled with swollen fibrin, it would make the fibrin shrink to the bottom in a few minutes, the change is so rapid. The reverse experiment can also be made. This very rapidity I consider one of the best arguments against the osmotic conception of edema. As a matter of fact, the most rapidly developing edemas observed clinically take more than minutes. One of the substances which is most markedly capable of influencing the affinity of fibrin for water is calcium. Calcium is about the only drug that ever does any good in many of the so-called urticarial diseases. Since urticarial eruptions are essentially local edemas, is it not probable that through administering calcium salts by mouth, we increase the calcium content of the tissues and thereby lessen the tendency of the tissues toward a development of these local edemas?

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THE DIURETIC ACTION OF ADRENALIN AND THE ACTIVE PRINCIPLE OF THE PITUITARY GLAND.

E. M. HOUGHTON, PH.C., M.D.,
AND
C. H. MERRILL, M.D.
DETROIT.

Many speculations have been indulged in by scientists to account for the physiologic function of the pituitary gland. This is especially true of the posterior or infundibular portion which in the human being is connected by a stalk with the tip of the infundibulum, and embryologically is to be regarded as an outgrowth from this part of the brain. This portion of the pituitary body, according to Berkeley, is very complex in its histologic structure; it contains many nerve cells, neuroglia tissue and a large quantity of glandular-like epithelial cells, which are so arranged as to form elongated vesicles or tubes, some of which contain a colloidal material. This structure suggests a secretory function.

Several writers have demonstrated by physiologic experiments that when extracts of this tissue are injected into the vein of anesthetized animals certain interesting changes occur in the circulatory system. Some of the earlier experiments were contradictory, but the experiments of Howell have often been confirmed by others and repeatedly by ourselves.

The action produced is very similar to that following like administrations of adrenalin. The blood pressure is markedly raised chiefly by peripheral stricture. In the case of adrenalin this action is very transient, while with the pituitary material the blood pressure remains

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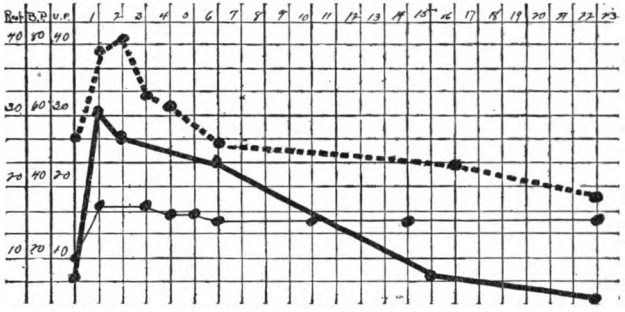

Fig. 1.—Chart showing results obtained from adrenalin. The figures in the three columns to the left indicate the respiratory rate, blood pressure in mm. Hg and urinary flow in drops, respectively. Dots indicate when observations were made. Broken line, blood pressure; light line, respiratory acceleration; heavy line, increase in ureteral flow.

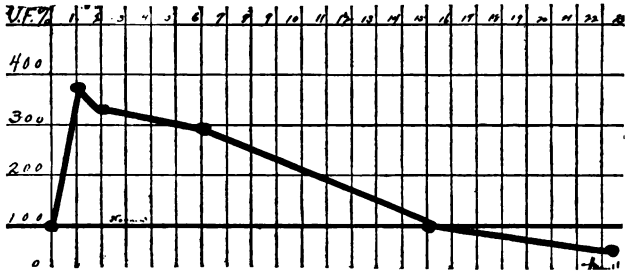

Fig. 2.—Chart showing average urinary curve for five dogs receiving .00001 gm. adrenalin in 5 c.c. saline solution and injected into the femoral vein. Figures at the left show percentage of increase of urinary flow. Figures at top indicate minutes.

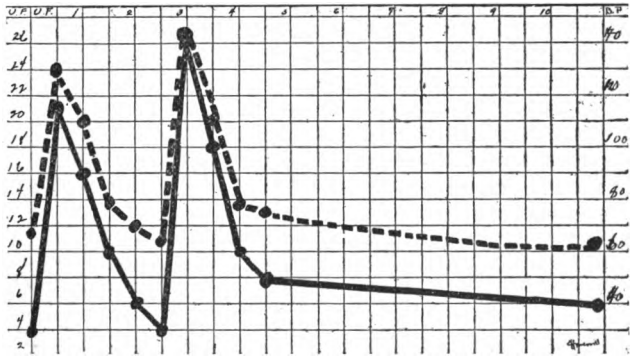

Fig. 3.—Chart showing that the increase in urinary flow (heavy line) follows very promptly on the repetition of the dose of adrenalin. The broken line indicates the blood pressure; the injection were made at 0 and at 2½.

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elevated much longer, in some cases a half hour or more. Howell points out the fact that repeated injections were followed by less and less rise of blood pressure until finally there was practically no response at all. This is well brought out in Figure 8. The pulse rate is slowed even when the vagi are cut or atropin has been administered, and the heart beats stronger than before.

For the experiments outlined in this paper we have employed an extract prepared by our colleague, Dr. T. B. Aldrich, using the method given in a paper read before the American Physiological Society, which he describes as follows:

PREPARATION OF EXTRACT OF INFUNDIBULAR BODY.

The infundibular portion of the pituitary body is carefully separated from the hypophysis cerebri and ground to a very fine pulp. To this, which constitutes about 8 per cent. of the weight of the moist gland, acidulated water (twelve times its weight) is added, and the mixture gradually heated to about 90 C. A portion of the proteid matter is coagulated by this procedure and removed by filtration. The remaining proteid, together with the phosphates, is removed for the most part with a solution of uranium acetate. The filtrate is practically without color and free from proteid. It represents the extract that has been used in the physiological experiments. One c..c of such an extract, when injected intravenously into a dog, causes a rise of from 15 to 45 mm. of mercury and represents 0.1 gm. of moist infundibular body or 0.01 gm. of dry. Since there is considerable inorganic matter present, the active body in 1 c.c. must be much less than the above. I think I am safe in saying that the active substance in 1 c.c. of such an extract is not more than 1/32 of a grain. In all my experiments, extending over some months, in which thousands of glands have been used, I have found such extracts, for the most part, very uniform in their physiologic action when injected intravenously.

From this concentrated extract Aldrich also reported having obtained a crystalline picrate and a sulphate in solution, which were found extremely active in producing a rise in blood pressure. We have conducted extensive experiments which showed positively that this material is practically non-toxic when given internally

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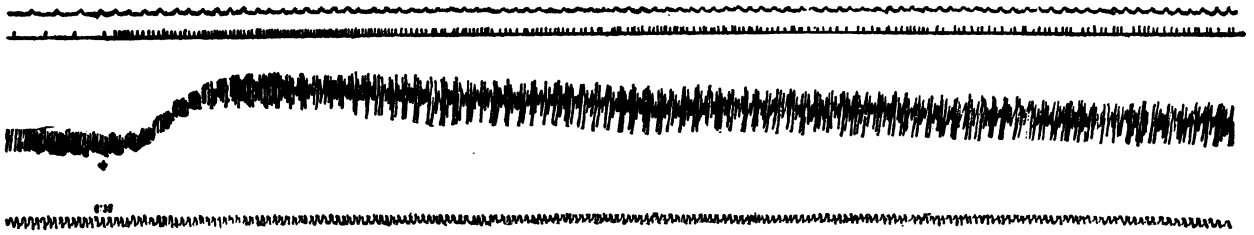

Fig. 4.—A typical kymographic tracing from which the analytical charts have been prepared. Top line, respiration; second line, water flow; third line, blood pressure; bottom line, time in seconds.

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or injected subcutaneously into guinea-pigs or rabbits or injected into the abdominal lymph sac of frogs.

The purpose of this paper, however, is to consider more especially the influence of the pituitary material on the secretion of urine. Professor Shafer in a recent paper makes the following statements:

INFLUENCE OF PITUITARY MATERIAL ON URINE SECRETION.

Pituitary extracts contain another hormone, the action of which is even more interesting than that which affects the heart and vessels. This second hormone has been found by Dr. Herring and myself to have a specific effect on the functions of the kidneys and to promote a free flow of urine—even if, as is often the case with animals under anesthesia, the urine may for a time have ceased to flow. Preceding or accompanying this increased flow of urine the kidneys expand, owing to the dilatation of the arterioles, so that the pituitary extract, while producing vascular constriction throughout the body generally, produces in the kidney vessels the opposite effect. This by itself must greatly assist the formation of urine.

But it is certain that, apart from the physical assistance to the formation (filtration) of urine derived from the increase of blood pressure and blood flow within the kidney, which it produces, pituitary extract also has a specific exciting effect on the cells which secrete the urine. In other words, although ordinarily accompanied and aided by a rise of general arterial pressure, due to general arterial constriction, and by expansion of the kidney vessels, due to local dilatation, the increased secretion of urine is essentially due to the glandular cells of the organ being stimulated to activity by the agency of a specific hormone.

This is proved by the fact that if a "repeat dose" of pituitary extract be given—which, as we have seen, is inactive so far as the rise of blood pressure is concerned—marked increase in the rate of flow of the urine can still be obtained. This may be accompanied by dilatation of kidney vessels, but, on the other hand, such dilatation may not occur at all—so that it is clear neither the kidney dilatation nor the rise of blood pressure are essential to the diuretic effect of pituitary extracts, which is due, therefore, to the presence of a special hormone. . . . That the internal secretion of the pituitary acts normally in promoting the functions of the kidneys there can be little doubt. This is, indeed, confirmed by the

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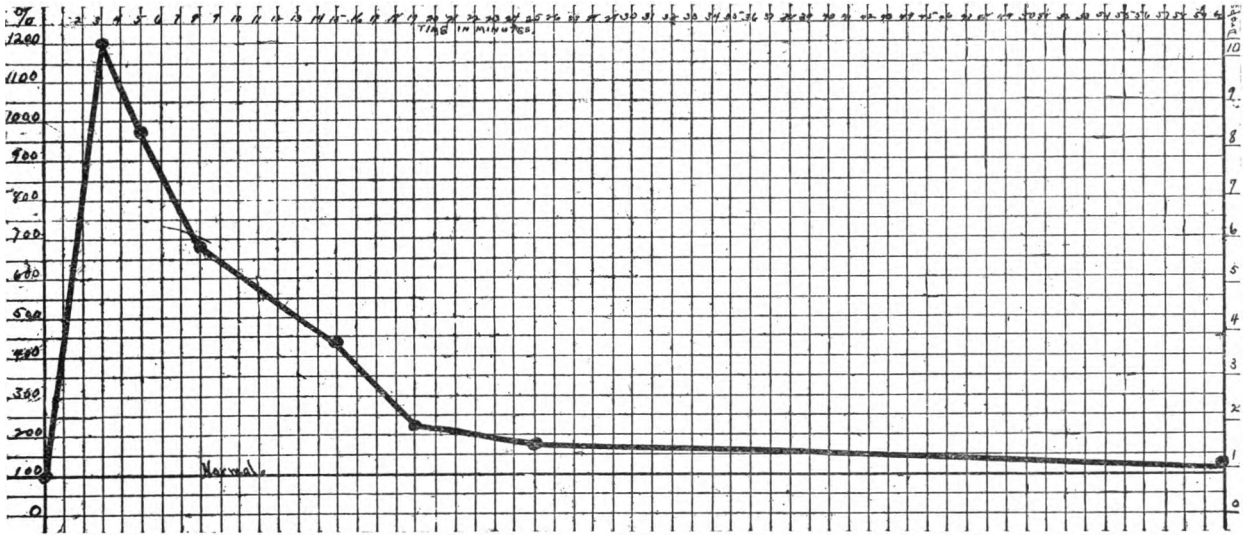

Fig. 5.—Chart showing the average urinary flow from five dogs receiving the pituitary extract in the vein. Figures at the left, percentage of increase; those at the top, time in minutes.

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frequency with which polyuria is mentioned as a symptom in cases where the pituitary has, on postmortem examination, been found to be enlarged.

DETERMINATIVE EXPERIMENTS.

Three series of experiments were undertaken to determine if possible the reason for the diuretic action produced by the active substances of the infundibulum as reported by Shafer.

Observations were made on the excretion of urine by two normal individuals, care being taken during the periods of observation, which extended over several days, that the food, drink and habits and the periods of work, exercise, etc., should be the same. After the normal excretion of urine had been determined by careful observation, relatively large doses of the pituitary extract were given internally, with the result that, apparently, there was a slight increase in the amount of urine voided during the periods of observation, which corresponded to those of the normal. The results, however, were inadequate to establish the positive fact that the material produces any marked diuretic influence on persons in health. Observations were likewise attempted on dogs, but the results were even more irregular than those obtained in the experiments on human beings, so it was concluded necessary to make additional observations by more refined laboratory experiments. Owing to many interruptions, however, and absence from the laboratory on pressing matters, the experiments have not been as exhaustive in character as was at first intended; in fact, this report may be looked on as one of progress merely to be amplified and completed by subsequent work.

A series of dogs were anesthetized by morphin and chloretone. Cannulæ were placed in the ureters for measuring the outflow of urine from the kidneys, the individual drops being recorded on the kymograph (Fig. 4) through electric connection.[1] The carotid artery

1. See explanation accompanying the chart in Figure 4.

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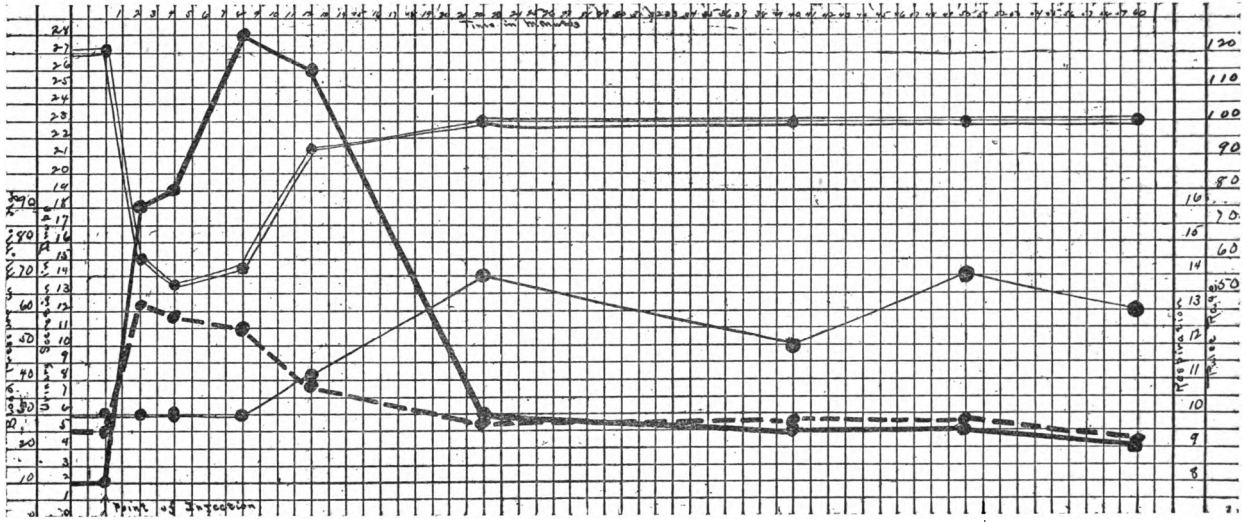

Fig. 6.—Chart showing the result of one experiment with pituitary extract on the respiration, blood pressure, pulse rate and urinary secretion of an anesthetized dog. The numerical values of the tracing are indicated at the right and left sides of the sheet. Heavy line, ureteral flow; broken line, blood pressure; light line, respiration; double line, pulse.

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was connected with a mercury manometer so that records could be made directly on the drum of the kymograph (Fig. 4). The respiratory movements were also recorded on the kymograph (Fig. 4). The three connections were not made in all of the experiments, as it was deemed unnecessary.

Reference to Figure 4 will show the manner of recording the experiments. The upper tracing is the record of the respiratory movements. It was intended only to register the number—not the character—of the respirations. Immediately below, a tracing records the drops of urine flowing from the ureteral cannula, each perpendicular stroke indicating a drop of urine. The next tracing below is the record from the carotid artery. At the bottom is the time record in seconds. Immediately above the actual time of the observation is recorded in numerals. The experiments showing the action of adrenalin and pituitary extract were carried out in precisely the same manner.

The chart in Figure 1 indicates in a characteristic way the results as obtained from adrenalin, being transferred from the kymograph sheet to the tracing cloth and the analytical data expressed in numerals. The three columns of figures at the left-hand side of the sheet indicate the respiratory rate, urinary flow in drops and blood pressure in millimeters of mercury, respectively. The figures at the top of the sheet indicate the time from the beginning of the experiment in minutes. The dots on the lines indicate the time at which observations were made. It will be observed that the blood pressure (broken line) rose very sharply from 56 to 88 millimeters of mercury, but within six minutes from the beginning of the experiment had fallen back to normal. This is characteristic of the blood-pressure action of adrenalin when administered intravenously. The light line indicates the respiratory acceleration. The heavy line shows the increase in ureteral flow from 8 minims per minute to 30 minims per minute, the maximum

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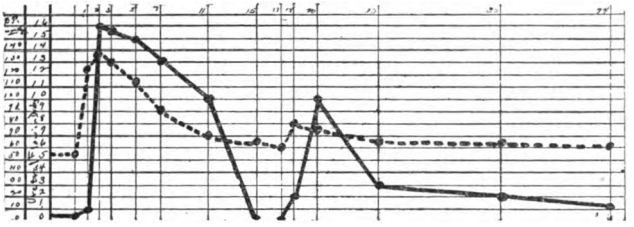

Fig. 7.—Chart showing the action of pituitary extract in repeated doses. Note that the blood pressure rises much less after the second injection, while the increase in urinary flow is very marked, but still less than after the primary injection. Heavy line, ureteral flow; broken line, blood pressure; injections at 0 and 17 mins.

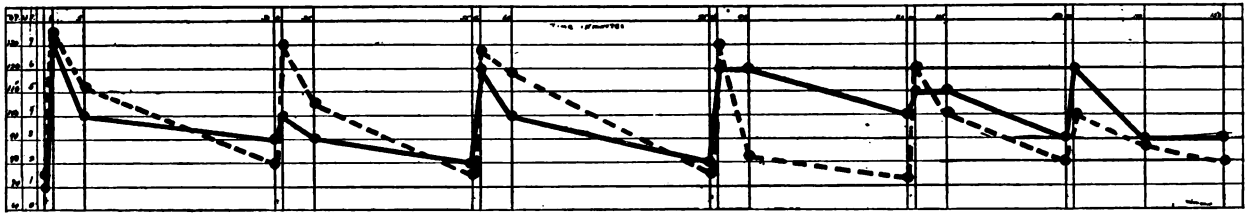

Fig. 8.—Chart showing the effect of repeated intravenous injections of pituitary extract on the blood-pressure and urinary secretion of anesthetized dogs. Heavy line, ureteral flow; broken line, blood-pressure; injections at 0, 31, 55, 85, 110, 130 minutes.

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increase in flow corresponding fairly closely in time with the maximum blood pressure. The increase in urinary flow, however, continues for a much longer time than the increase in blood pressure, at the end of fifteen minutes the flow being approximately the same as at the beginning of the experiment.

The chart in Figure 2 shows the average urinary curve for five dogs receiving administrations of 1/100,000 of a gram of adrenalin dissolved in 5 c.c. of saline solution and injected into the femoral vein. The figures at the left-hand side of the sheet indicate the percentage of increase of the urinary flow, while the time from the beginning of the experiment in minutes is given at the top.

It will be observed from the charts in Figures 1 and 2 that the increase in the flow of urine corresponds quite closely to the rise in blood pressure but that the flow continues above normal for some minutes after the blood pressure has reached normal.

TABLE 1.

SHOWING EFFECT OF INTRAVENOUS INJECTION OF PITUITARY EXTRACT.

Time.	B.P. in mm. Hg.	Pulse per per min.	Resp per per min.	Urine, drops per min.
Normal	30	96	6	5
8:35*	..	..	..	..
8:35½	55	84	10	52
8:36	63	74	14	62
8:40	45	66	14	28
8:45	36	74	10	26
8:50	33	78	8	18
8:55	32	92	8	14
9:00	32	98	10	12
9:05	32	104	10	10
9:15	31	108	8	6

* At 8:35, 2 c.c. pituitary extract injected intravenously.

Experiments were undertaken after the technic of Sollmann[2] to determine the action of the pituitary extract on the secreting cells of the isolated kidney. Cannulas were placed in the renal vein and ureter and determinations made of the flow of blood from the cannula in the vein and the amount of urine secreted and flowing from the cannula in the ureter, record being

2. Am. Jour. Physiol., February, 1908.

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kept from time to time. The kidneys were placed in a saline solution kept at body temperature; likewise, the fluid for perfusing the kidney was warmed beforehand; apparatus was arranged so that perfusion could be carried out at 50 and 100 mm. of mercury pressure; the experiments being undertaken to determine whether the pituitary extract had a specific influence on the secreting cells of the kidney or whether the increased flow of urine observed in animals receiving intravenous injections of pituitary extract was merely dependent on the increased blood pressure produced. The following tables will give the details of the experiments:

TABLE 2.

Time.	Ureteral Flow.	Venous Flow in Minims per Minute.
10:00	A. Kidney perfused with 1 per cent. saline at 50 mm. mercury pressure.	
10:01	.....	14
10:03	.....	14
10:06	4 minims per minute.....	10
10:21	B. Pressure raised to 100 mm. mercury.	
10:21	12 minims per minute.....	50
10:24	11 minims per minute.....	25
10:27	C. Pituitary extract, 1½ mg. to 0.0015 gms. per c.c. of saline. Pressure 100 mm. mercury.	
10:28	12 minims per minute.....	20
10:31	6 minims per minute.....	26
10:36	5 minims per minute.....	21
10:37	D. Blood pressure lowered to 50 mm. mercury.	
10:39	2 minims per minute.....	35
10:40	1 minim per minute.....	20
10:42	E. Saline, 1 per cent., used instead of pituitary extract solution.	
10:44	Zero	12
10:48	Zero	12
10:49	F. Pituitary extract added as before.	
10:51	Zero	12
10:58	Zero	8½
11:01	Zero	8½
11:05	G. Raised pressure to 100 mm. mercury.	
11:06	Zero	25
11:07	3 minims per minute.....	56
11:14	3 minims per minute.....	45
11:17	3 minims per minute.....	35
11:22	H. Pituitary extract withdrawn and 1 per cent. saline introduced.	
11:22	3 minims per minute.....	40
11:23	3 minims per minute.....	40
11:33	2 minims per minute.....	30
11:43	4 minims per minute.....	42
11:45	4½ minims per minute.....	46
12:44	I. Pituitary extract added as before.	
12:47	4 minims per minute.....	80
12:50	4 minims per minute.....	90
1:05	2 minims per minute.....	100
1:35	1 minim per minute.....	100
1:41	J. Saline, 1 per cent.	
1:55	1¼ minims per minute.....	96

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TABLE 3.

Time.	Ureteral Flow.	Venous Flow in Minims per Minute.
3:30	A. Saline, 1 per cent., at 100mm. mercury pressure.	
3:31	18 minims per minute	36
3:34	12 minims per minute	30
3:36	12 minims per minute	26
3:37	B.—D. F. Blood at 100 mm. mercury pressure.	
3:38	.....	24
3:40	4 minims per minute	16
3:45	5 minims per minute	10
3:46	8 minims per minute	12
3:46½	4 minims per minute	12
3:50	4 minims per minute	10
3:55	4 minims per minute	10
4:00	3½ minims per minute	14
4:05	3½ minims per minute	14
4:10	2½ minims per minute	14
4:25	1½ minims per minute	12
4:26	C. Lowered to 50 mm. Mercury pressure.	
4:30	Practically blocked.	
4:35	.....	2
4:38	.....	1½
4:40	D. Pituitary extract at 50. mm. mercury pressure.	
4:45	1¼ minims per minute	1⅛
4:50	2 minims per minute	3
4:55	1⅛ minims per minute	5
5:00	E. Pituitary extract at 100 mm. mercury pressure.	
5:01	3 minims per minute	40
5:05	2½ minims per minute	50
5:10	2½ minims per minute	46

TABLE 4.

Time.	Ureteral Flow.	Venous Flow in Minims per Minute.
10:20	A. Saline, 1 per cent., at 50 mm. mercury pressure. Perfusion of fresh kidney.	
10:23	.....	6
10:27	.....	5
10:32	1½ minims per minute	5
10:40	1½ minims per minute	6
10:45	1½ minims per minute	5½
	B. Raised to 100 mm. mercury pressure.	
10:46	6 minims per minute	75
11:00	1 1/5 minims per minute	15
11:05	1 1/5 minims per minute	..
	C. Lowered to 50 mm. mercury pressure.	
11:09	.....	7½
11:25	1 minim per minute. (Flow very slow both sides.)	
11:33	D. Pituitary extract. 50 mm. pressure. (1 mg. to 3 c.c., 1 per cent. Saline.)	
11:35	1 1/5 minims per minute	..
11:40	1½ minims per minute	7
11:41	E. Raised to 100 mm. mercury pressure.	
11:42	4 minims per minute	15
11:45	5 minims per minute	15
11:54	5 minims per minute	15
11:55	F. Lowered to 50 mm. mercury pressure.	
11:56	2 minims per minute	6½
12:00	1¼ minims per minute	6
12:05	1 1/5 minims per minute	5

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From these tables it will be observed that at 50 mm. mercury pressure a 1 per cent. physiologic salt solution produces but a slight flow of urine through the ureter. When the pressure is increased to 100 mm. mercury, both the urethral and venous flow is markedly increased. The same general fact is observed when pituitary extract is added to the saline perfusion, but the urethral and venous flow is less, both at 50 mm. of mercury and at 100 mm. of mercury than where saline alone is used.

CONCLUSIONS.

From these experiments it would seem to us that the explanation of the increased urinary flow in anesthetized animals depends chiefly on the increase in blood pressure produced by the intravenous injection of the adrenalin solution or the pituitary extract in solution rather than on a specific action on the secreting cells of the kidney. It is possible, however, that a specific action on the kidneys occurs, but if so it is less marked than in the case of the 1 per cent. saline solution.

Macroscopic observation of the perfused kidney indicated that there was considerable enlargement of the organ while the experiments were being carried out. This would assist in the more rapid secretion of urine, especially if accompanied by increased pressure, but, as just stated, there is not the same degree of relaxation or dilatation of the blood vessels in the kidney as follows the perfusion with the saline itself. This is as we would expect, since experiments on the web of the frog, on the inflamed conjunctiva of the rabbit and other animals show positively that the pituitary extract does narrow the caliber of the arterioles.

If the pituitary extract possesses, as Shafer believes, the specific secretory effect, it would seem to us that it should manifest itself by greatly increased flow of urine when brought in contact with the secretory cells of the kidney. If it does have this specific action it has it to a much less degree than sodium chlorid itself.

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HISTOPLASMOSIS: A FATAL INFECTIOUS DISEASE RESEMBLING KALA-AZAR FOUND AMONG NATIVES OF TROPICAL AMERICA.

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ANCON, CANAL ZONE, PANAMA.

INTRODUCTION.

Histoplasmosis[1] is a term applied to a fatal infection by a protozoon, *Histoplasma capsulatum,* which has been encountered three times during the past two and one-half years in Ancon Hospital, Canal Zone, Panama. Clinically and pathologically the disease is suggestive of kala-azar,[2] a disease of India, characterized by irregular fever, emaciation and splenomegaly and by the presence of the Leishman-Donovan body in the tissues. The micro-organism responsible for the Isthmian infection is different from the Leishman-Donovan body, sufficiently so to warrant its being placed in a different order.

The condition was not discovered until the autopsies, and chiefly on that account cultural experiments were unsuccessful and clinical data meager.

HISTORICAL SKETCH.

Cunningham[3] published in 1885 an account of bodies found in the tissue obtained from a Delhi boil. Cunningham's technic was crude and the bodies measured 8.8 to 12.6 microns—altogether too large to be the bodies described later by Wright in a tropical ulcer called "Delhi sore."

In 1903 J. H. Wright[4] described micro-organisms found in smears and sections of tissue from an ulcer of the cheek. The patient was a native of Armenia, nine years of age. The ulcer had made its appearance some two or three months before the child left Armenia.

1. Darling, S. T.: Maryland Med. Jour., April, 1907.
2. Rogers, Leonard: Fevers in the Tropics, Oxford Med. Publ., London, 1908.
3. Cunningham, D. D.: Scientific Memoirs by Medical Officers of the Army of India; Part I (1884), Calcutta, 1885.
4. Wright, J. H.: Jour. Med. Research, December, 1903, x; new series, v, 472-482.

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"The lesions consist essentially of a very extensive infiltration of the corium and papilla by cells accompanied by atrophy and disappearance of the epidermis of the part. The infiltrating cells are plasma cells, various kinds of lymphoid cells and large cells with single vesicular nuclei and a relatively large amount of cytoplasm in which are large numbers of micro-organisms.

"The micro-organisms in smears are generally round, sharply defined in outline, and two to four microns in diameter. A large part of their peripheral portion is stained a pale robbin's-egg blue, while their central portions are unstained or white. A very prominent feature is the presence in each of the bodies of a larger and smaller lilac-colored mass. The larger mass is about one-fourth or one-third the size of the body; is of variable shape, but always forms a part of the rounded periphery of the body.

"The blue peripheral portions of the bodies are usually sharply defined from the central unstained portion and sometimes show small unstained areas. A few of the bodies are oval or elongate in form." Wright proposed the name *Helcosoma tropicum* for the parasite.

Major Leishman,[5] R.A.M.C., described in May, 1903, certain small oval bodies obtained from autopsy spleen smears in a case of chronic dysentery, cachexia and low fever. Leishman had observed this body first in 1900. The patient had contracted the disease in Dum-Dum, near Calcutta, and died in London. Leishman described the bodies as being round or oval, and two to three microns in diameter. When stained by the Rowmonowsky method they were found to contain two masses of chromatin, a large circular mass or ring and another smaller mass usually in the form of a short rod set perpendicularly or at a tangent to the circumference of the larger mass. The outline of the bodies containing these two masses was faintly visible with the stain. They existed in large number in the spleen cells. In Major Leishman's opinion the bodies were residues of trypanosomes.

In July, 1903, Captain Donovan,[6] I.M.S., reported having found the same bodies in autopsy spleen smears from three consecutive cases said to have died of chronic malaria in Madras. Later he recovered them from the spleen of a boy suffering with an irregular fever.

Marchand and Ledingham[7] published in 1904 an account of a case

5. Leishman, W. B.: Brit. Med. Jour., 1903, i, 1252; 1903, ii, 1376; 1904, i, 303.

6. Donovan, C.: Brit. Med. Jour., 1903, ii, 79, 1401; Indian Med. Gaz., 1904, p. 321.

7. Marchand and Ledingham: Ztschr. f. Hyg. u. Infectionskrankh., May, 1904.

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of kala-azar in a German soldier who had become infected while with his regiment in China and who died in Leipsic. Marchand observed the bodies in the tissues in this case late in 1902 or early in 1903.

Ronald Ross[8] has contributed to our knowledge of kala-azar and the Leishman-Donovan body, and has named the latter *Leishmania Donovani,* believing it to belong to a new genus of *Sporozoa.*

Laveran[9] examined Donovan's preparations and placed the organism with the *Piroplasmata,* calling it *Piroplasma Donovani.*

Strong[10] in 1906 described an intracellular body found in a tropical ulcer in Manila; that body may belong to the group described here.

The zoologic status of the Leishman-Donovan body was more closely defined by Leonard Rogers,[11] who succeeded in cultivating the body in citrated blood from a spleen puncture in the cold. The bodies became flagellated. Rogers' cultural work has been confirmed by Christophers.[12]

Captain Patton,[13] I.M.S., has made the highly important observation that developing Leishman-Donovan bodies in all stages may be found in infected bed-bugs, *Cimex rotundatus* (*C. macrocephalus*). He has also added to our knowledge of flagellates resembling the Leishman-Donovan body by his researches on *Herpetomonads* parasitic in insects. Captain Patton[14] has shown that a herpetomonas of *Culex pipiens* has a stage exactly similar to the human stage of the parasite of kala-azar, and another herpetomonas[15] in the Lygaeid bug, *Lygaeus militans* (Fabr.), which is almost identical with the parasite of kala-azar. This parasite passes its complete cycle in the intestinal tract of the bug.

On December 5, 1905, I performed an autopsy[16] on a negro Martiniquan, who had died at Ancon Hospital, Canal Zone, Panama. On examining smears from a peculiarly white atypical tubercle in the lung and from the spleen, liver and bone marrow I observed an intense invasion of large endothelial-like cells by small round or oval micro-organisms.

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8. Ross, Ronald: Brit. Med. Jour., 1903, ii, 1261 and 1401; 1904, i, 1049.
9. Laveran, A., and Mesnil, F.: Compt. rend. Soc. de biol., Par., 1904, cxxxvii, 95; cxxxviii, 187.
10. Strong, R. P.: Philippine Jour. Sc., 1906, i, No. 1.
11. Rogers, Leonard: Lancet, London, July 23, 1904, ii; Quart. Jour. Micros. Sc., November, 1904, xlviii, Part 3.
12. Christophers, S. R.: Scientific Memoirs by the Officers of Medical and Sanitary Departments of the Government of India, Calcutta, 1905, new series, No. 15.
13. Patton, W. S.: Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India, new series, Nos. 27 and 30.
14. Patton, W. S.: Brit. Med. Jour., 1907, ii, 78.
15. Patton: W. S.: Personal communication to be published later.
16. Darling, S. T.: Jour. Am. Med. Assn., 1906, xlvi, 1283

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Drawings showing various specimens of *Histoplasma capsulatum* from the spleen of Patient 3 (× 1600).

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The bodies had definite refractile peripheries and their internal structure was not uniform or homogeneous. They were about three microns in diameter.

This was the first time in the New World that an organism of this type had been found responsible for a fatal infection in a native of the New World; and, so far as I have been able to learn, the organism described here and in two preliminary reports has never been seen or described before. Maj. Ronald Ross regards it as a protozoan organism, resembling somewhat the Leishman-Donovan body, but differing from it chiefly in not containing the chromatin rod usually seen in the Leishman-Donovan body. Wright's *Helcosoma tropicum* was obtained from a native of the Levant, recently arrived in Boston.

ACCOUNT OF THREE CASES.

CASE 1.—*Patient.*—C. D., Hospital No. 7715. Negro from Martinque, aged 27; occupation carpenter; residence, Paraiso, a village in the Canal Zone.

History.—The patient had been a resident of the zone three months. While in Martinique he had suffered from some mental disturbance. His present illness dates from Sept. 15, 1905, when he complained of fever and vomiting.

Condition on Admission.—On entering Ancon Hospital Dec. 5, 1905, mildly delirious and incoherent. Lungs clear. Abdomen scaphoid. Spleen enlarged. Blood: negative for malarial parasites; leucocytosis 2,200; hemoglobin, 60 per cent. (Dare's). Feces negative. Temperature: On admission, Dec. 5, 1905, 12:30 p. m., 101; pulse 120. December 6, 8 a. m., temperature, 95; pulse, 96. 4 p. m., temperature, 98; pulse, 100.

Autopsy.—The patient died December 6, 11:30 p. m. The autopsy was made on December 7, 8:30 a. m.

Macroscopic and Microscopic Examination.—Body of negro, moderately emaciated; length, 5 feet, 8¾ inches; inter-nipple distance, 7 3-16 inches; rigor mortis was plus. The odor on opening the thorax was suggestive of pulmonary tuberculosis. The right and left pleura were free. There were numerous red blotches (ecchymoses) beneath the visceral pleura of both lungs, 8 mm. in diameter. Many small nodules could be felt under the visceral pleura. The lungs on section were found studded with pale gray hyaline miliary tubercles from 2 to 3 mm. in diameter. The lungs were heavier and more voluminous than normal. The tubercles were not as closely packed or as numerous as is often found in miliary tuberculosis, and the general color of the lungs was bright red. The peribronchial lymph nodes contained a few small soft recently caseated tubercles. The nodes were enlarged and pigmented. The heart was small and normal. The liver was enlarged and pale, and there was slight atrophic cirrhosis. The spleen was enlarged to three times the normal in size; the pulp was very firm. The Malpighian bodies were distinct. Here and there were a number of small yellow nodules resembling tubercles. In the kidneys there were a few depressions in a cortex diminished to 8 mm. in depth. The pancreas and bladder were normal, and the rib bone marrow normal and dry. Examination of the brain showed the pia-arachnoid slightly edematous and more generally adherent to the cortex than normal. The calvarium was very thick. Several specimens of *Tricocephalus dispar* were found in the cecum. There were a few small superficial circular ulcers from 2 to 4 mm. in diameter in the cecum and ileum. The mesenteric lymph nodes and those at hilum of the spleen were enlarged and pale.

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Bacteriologic Examination.—Spleen smears were negative for malarial parasites or pigment. Oval and round bodies were free in the plasma. In the rib bone marrow smears, there were traces of intracellular malarial pigment. A number of bodies similar to those in the spleen were seen. In lung smears tubercle bacilli were absent. There were myriads of intracellular and extracellular bodies similar to those found in the spleen and the marrow. A moist coverslip preparation from the intestinal ulcers showed motile amebas.

Anatomic Diagnosis.—Acute miliary tuberculosis, pulmonary type. Tuberculous lymphadenitis, peribronchial. Chronic interstitial splenitis. Atrophic cirrhosis. Chronic interstitial nephritis, slight. Lymphadenitis, mesenteric. Chronic leptomeningitis. Edema of pia-arachnoid. Ulcerative enterocolitis. Amebiasis. General infection by protozoon.

The micro-organism was not discovered in smears until later in the day, after the anatomic diagnosis had been made.

Appearance of the Parasite in Smears.—Lungs: This specimen was stained by carbolfuchsin and Gabbet's methylene blue, overstained with polychrome methylene blue, and differentiated with eosin. The polychrome blue was prepared as follows:

	gm.
Methylene blue, pure medic. Grüb	1.
Sodium carbonate, pure	.5
Distilled water	100.

This was placed in the thermostat one week, and kept at room temperature for six months. The excess of blue was removed by washing the smear alternately with alcoholic solution of eosin (0.5 per cent. in 60 per cent. ethyl alcohol) one second and distilled water a few seconds, until the internal structure of the parasite showed plainly. The parasite was oviform or round and was surrounded by a clear, refractile, non-staining rim, in thickness about one-sixth the diameter of the parasite. This refractile rim was present in all smears, whether previously treated with acid blue or not. The structure was not homogeneous, but consisted of a faintly staining substance and a deeply staining one; a clear space or spaces; and chromatin granules. The chromatin granules were generally single; sometimes two or more were counted. One large parasite appeared to have six such dots of chromatin. The granules were often situated in a clear non-staining zone at one side of the darker staining substance; at other times they were situated on the margin or within this substance, and also frequently appeared in the clear refractile capsule. The chromatin granules were generally dot-shaped, very rarely elongated. Occasionally two chromatin dots placed together simulated a rod form.

The clear space or spaces resembled vacuoles; at times they resembled the clear non-staining spaces seen in filaria embryos and trypanosomes. The staining substance almost entirely filled the capsule or refractile rim of the parasite. The circular contour of the staining substance was at times broken on one side by the clear non-staining zone. This zone varied in shape, size, and in its relation to the staining substance, being circular, oval, or irregular in form; being three-fourths the size of the entire parasite, or at times barely perceptible on account of its minuteness; being centrally located or eccentric; and being single or multiple—two or three.

In size the parasites were from one to four microns through their greatest diameter; commonly this diameter was three microns.

The parasite appeared to divide by fission into two equal or unequal elements. One parasite appeared to be dividing into four equal elements. Several parasites with chromatin dots scattered through their substances appeared as presegmenting bodies, ready to divide into five or six elements. Occasionally a smaller para-

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site might be seen close beside a larger one, as though separating from it; the smaller one being about one micron in diameter.

Although oval or round in outline, the staining substance, together with the clear, non-staining zone and chromatin granules, gave a varying picture, depending on the point of view. Forms suggesting the appearance of familiar objects, such as the eye, a shield, a conch shell, a bullet, or a shuttle, were seen. The resemblance of the deeply staining substance in certain parasites to a mammalian embryo in "fetal attitude" was very striking.

In the lung smears the parasite was apparently always intracellular and the cells contained from ten to one hundred or more parasites. The appearance of free parasites was probably due to the squeezing and breaking up of infected epithelial cells by pressure in making the smear. One unbroken alveolar epithelial cell occupied one-third the diameter of the field (1/12 oil im. No. 1 oc. B. & L.). Parasites had invaded the cell nucleus as well as the cytoplasm, and it was estimated that this cell contained more than three hundred.

Spleen and rib marrow smears showed fewer parasites, two or three to a field, and they appeared to be extracellular. The nucleus of a spleen or marrow cell appeared now and then to have been invaded. Each parasite had a definite refractile rim, as in the lung smears, and its internal structure could be well made out. Red blood corpuscles were never invaded.

Three flagellated forms were seen in a lung smear. The distal extremity of one of the flagella contained a rod of chromatin placed at right angles to the flagellum, simulating the relation of centrosome to chromatin filament in *Trypanosoma Lewisi*. The flagella were single, short and thick, without chromatin filaments, and were enclosed by the refractile capsule, continuous with that of the body of the parasite.

Examination of Sections.—Sections were fixed in Zenker's solution and stained by eosin and hematoxylin, Van Giesen's method, and polychrome-methylene blue.

Lung: The alveolar capillaries were tortuous and engorged with red blood corpuscles. In places the walls were broken down, stretched, or greatly distended. No leucocytes were seen within the capillaries. The epithelial cells of the alveolar walls was desquamating or completely shed. The alveoli were seen to be filled with red blood corpuscles, generally having a washed-out appearance; red blood corpuscles and serum; or red blood corpuscles, serum, and large swollen alveolar epithelial cells containing many parasites.

Polymorphonuclear leucocytes were rarely observed in the alveolar contents; a few mononuclear elements were noted. There were no tubercles. The pseudo-tuberculous areas were made up of alveoli with broken, distorted, or collapsed walls, containing many alveolar epithelial cells, distended by parasites. Small vessels or capillaries were seen to pass through the pseudo-tubercles, but there were no evidences of the hemorrhages seen in other alveoli. Within these areas there were enormous numbers of parasites generally contained within epithelial cells—rarely free. The nuclei of invaded cells stained well, though often more faintly than normal. The cytoplasm of badly infected cells was wanting, and there were numerous distended epithelial cells devoid of cytoplasm and parasites. The infected cells had a distinctly staining rim of cytoplasm, even when their nucleus and cytoplasm was gone.

Liver: There were numerous faintly staining areas ranging in size from that of a single liver cell to those one-third the size of a lobule; in which the liver cells and endothelial cells of the portal capillaries were completely transformed by invading parasites. In the larger areas the cytoplasm and nuclei of the invaded cells had disappeared or did not stain. There was a mass of débris, embedded in which were myriads of parasites. In places the liver cells were normal; in others they had suffered cloudy change. In these latter localities

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there appeared to be a stasis of blood in the portal capillaries due to occlusion of capillaries by enormously distended endothelial cells filled with parasites.

There was a distinct primary invasion of liver cells in places, although oftener it seemed that many liver cells became invaded after they had had their nutrition cut off by infected overlying endothelial cells.

Around the portal space the connective tissue was increased in amount and there was a recent round cell infiltration. The bile ducts and their epithelium were normal.

Spleen: The splenic spaces were greatly engorged with red blood corpuscles. The connective tissue was moderately increased, its cells were swollen, cloudy, and at times contained parasites. There was cloudy swelling of mononuclear cells in small areas here and there, and many of these cells contained parasites. There were also numerous free parasites.

Lymph Node from Hilum of Spleen.—The cortical follicles and medullary cords of the dense lymphoid tissue were, with the exceptions noted below, normal. The capsule and reticulum throughout the node were the seat of degenerative changes. The reticulum of the loose lymphoid tissue enclosed many large mononuclear cells possessed of distinctly staining nuclei, and contained many parasites.

There were two cortical follicles, and portions of a medullary cord which had undergone cloudy swelling and necrosis, amid the débris of which were mononuclear cells containing parasites. The margins of these areas showed beginning degenerative changes; many fragmented nuclei were seen, as well as mononuclear cells distended by parasites.

Peribronchial Lymph Node.—This node contained several old fibrocaseous tubercles, and one giant cell. The reticulum and capsule of the node were greatly thickened in places. A lymph vessel beneath the capsule contained mononuclear cells infected by parasites.

CASE 2.—*Patient.*—G. B., Hospital No. 9141. Negro from Martinque; aged 29; occupation, laborer; residence, Corozal, a village in the Canal Zone. The patient complained of headache, vomiting and diarrhea. It was not known how long he had been ill or how long he had been a resident of the Isthmus. He presented a wasted appearance. His visible mucous membranes were pale. His spleen was palpable and his thorax negative. He was admitted to the hospital Jan. 9, 1906. Malarial parasites were present in his blood.

Clinical Course.—During the first week after admission the temperature was irregularly continuous, being about two degrees above normal. During the second week the temperature curve became regularly remittent; physical signs of pneumonia on the right side were apparent. On January 29, the day of his death, it was noted that the liver extended two finger's-breadth below the costal margin. The spleen extended to a similar depth and both spleen and liver were tender. The patient was conscious and coherent, and complained of pains in his legs and thighs. He lay on his back with his thighs flexed and complained of burning sensations in his feet. His calves were tender on the slightest pressure and his patellar reflexes were absent.

Autopsy.—This was made Jan. 30, 1906, 8 a. m., four hours after death. The body was 5 feet 7 inches in length and much emaciated. Rigor mortis was plus. Pleura free—negative. Peribronchial lymphnodes enlarged. Pericardium, negative. Omentum contracted. No peritonitis noted. Lungs: The upper part of the lower lobes showed patches of bronchopneumonia. The upper lobes were negative. Heart: Small, flabby. Right heart considerably dilated. Valves negative; muscles light in color. Liver: Normal in size; color reddish brown. Adrenals: negative. Kidneys: Somewhat enlarged. Their capsules stripped with ease and both were much congested. Spleen: Five times its normal size, firm. There was an increase in its fibrous stroma. Its pulp was deep brown in color and smears contained æstivo-autumnal malarial parasites. Intestinal

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tract: The stomach contained considerable quantity of coffee-ground material and the mucosa, while very pale, showed no indications of hemorrhage. The intestines contained round worms, whip-worms, and New World uncinaria worms.

Anatomic Diagnosis: Bronchopneumonia; acute parenchymatous nephritis; uncinariasis; ascariasis tricocephaliasis; malarial fever, e. a.

Smears from the spleen, bone marrow, liver and lymphnodes examined the following day showed numerous micro-organisms similar to those seen in Case I.

Histopathology.—Kidney: The convoluted tubules were generally distended. The nuclei of the epithelial cells were swollen and did not stain deeply. Here and there a nucleus was missing. The lumen contained coagulated albumin and an occasional desquamated epithelial cell. Some of the straight tubules contained hyaline casts. The epithelium of the convoluted tubules was generally flattened, not cuboidal. The convoluted tubules were widely separated by a cellular exudation or proliferation. The cells making up this exudate or proliferate had eosin-staining protoplasm and most of them had deeply staining nuclei, eccentrically placed. Minute hemorrhages were also noted in these interstitial places. The cells of the glomeruli and of Bowman's capsule were swollen and their nuclei were swollen and pale. A few convoluted tubules showed colloid degeneration. The vessels appeared normal. Heart and pancreas: Negative. Spleen: The splenic spaces were distended by red blood cells. Numerous mononuclear phagocytes containing malarial pigment were seen. A few of these phagocytes were dotted with parasites. The Malpighian bodies showed some disappearance of their lymphoid elements. Liver: There was a slight round-cell proliferation, around the portal spaces and in small foci here and there. The columns of liver cells everywhere appeared flattened and attenuated, but the capillaries were not engorged. There appeared to have been a diffuse disappearance of liver cells. There were some very small areas about the size of a dozen liver cells in which there was an almost complete disappearance of liver cells; the space being occupied by endothelial cells containing malarial pigment and occasionally parasites. Throughout the section there was much malarial pigment enclosed within endothelial cells lining the capillaries. Many of these endothelial cells were distended by parasites (*Histoplasma capsulatum*) as well as pigment. From this section the earliest lesion was apparently that in the endothelial cell. The areas of round-cell proliferation—apart from those around the portal spaces—were frequently associated on one side by the small areas of necrosis containing parasites. Some of these areas of necrosis extended outward from a portal space; others were in the intermediate zone; while others could not be oriented on account of the obscuration of the lobule outline. One of these small areas, where the liver cells had disappeared, contained a typical giant cell with a mural arrangement of its neuclei on one side. This giant cell was in the intermediate zone of a lobule. The giant cell was not a part of a tubercle, and around it were no round cells, epithelioid cells, or nuclear fragmentation. The structures in the portal spaces were normal. In this instance the infection was a mixed one of the malarial parasite and *Histoplasma capsulatum*. Adrenal: Negative. Lung: The capillaries were tortuous and engorged with red blood cells. The alveoli contained red blood cells and polymorphonuclear leucocytes in about equal numbers, also a few desquamated alveolar epithelial cells. No parasites were seen. Lymph Node: The spaces of the lymphoid tissue contained numerous large mononuclear phagocytes—some with double nuclei—many of which had engulfed red blood cells. There were no areas of necrosis, the changes being hyperplasia of large and small lymphoid cells. No parasites were seen in the section.

CASE 3.—*Patient.*—Fu Mas; Hospital No. 17,184; aged 55; a native of Canton, China; admitted to Ancon Hospital, Aug. 9, 1906.

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History.—From his closest friend the information was obtained that the patient came direct from Canton, China, to the United States. He had been living on the Isthmus during the last fifteen years, living at Bocas del Toro, near Colon, four or five years of this period. About six months before he died he was employed in a little shop near the hospital buildings at Miraflores. He had lived there five months when he removed to Panama one month before his death. His friend said that the patient had been going down hill physically for the five months preceding his death, that he had had fever, chills, slight emaciation, and that no dysentery or cough had been noticed. There had been no pigmentary changes of the skin or changes in the hair noticed, and so far as he knows there was no bleeding of the gums, but there had been some loss of strength.

Clinical Course.—His temperature on admission was 102, falling to 97.5 the following morning. His pulse ranged from 98 to 120 and the respirations from 18 to 30. The hemoglobin was estimated at 70 per cent. His blood was otherwise negative. In the afternoon of August 10 involuntary urination was noticed. The patient was said to have been in a peculiar coma, and slept all day, but could be aroused. Died, Aug. 10, 1906, 11:05 a. m.

Autopsy.—Aug. 11, 1906, eighteen hours after death. Body of male Chinese. Hair cropped short. Moderate pitting of feet, legs, thighs, lower abdomen and left side of face, which latter was congested. Rigor mortis was absent. There were three or four raised recent broad papules 8 mm. in diameter on the left arm, outer aspect. External genitalia normal. Scrotum not edematous. Subcutaneous tissues slightly edematous. Muscles of chest, abdomen and legs very pale. Sartorius muscles a dull gray color. The knee joints normal. Lungs: Voluminous and the pleura free. Right and left upper lobes and middle lobe contained a few raised hyaline dense areas resembling tubercles. They were from 2 to 6 mm. in diameter and were often irregular in contour and elongate. They were always surrounded by a raised hemorrhagic zone about 4 mm. in thickness. The peribronchial lymph nodes were slightly enlarged, pigmented black, and contained no tubercles. Pericardium normal, containing about 30 c.c. clear fluid. Heart: Rather small and flaccid; valves, normal; musculature dull brown color. Liver: Enlarged, capsule smooth. Organ presented a unique appearance, due to a grayish yellow arborescence. The limbs of the arborescence were 4 mm. in diameter and apparently followed portal radicals. Their centers were gray, their peripheries rather yellow. The areas contained only four or six limbs, but were scatttered thickly throughout the entire organ, save in one portion of the liver near the falciform ligament about 16 c.c. elongate anteroposteriorly. There was much fatty infiltration of the parenchyma. The gall bladder was normal. The portal lymph nodes were enlarged, pale, yellow, slightly edematous and friable. Spleen: Enlarged, long and relatively narrow; its pulp was firm, friable and dark red in color. Malpighian bodies indistinct. Capsule smooth and tense. Kidneys and Adrenals: Negative. The peritoneal surface of the sigmoid flexure, descending colon and perirectal peritoneum near Poupart's ligament was intensely pigmented black in spots. Aorta: Normal. Testes: Normal. The colon contained about twenty-four small 6 mm. round pigmented areas of hyperplasia and ulceration. Small Intestines: The entire ileum and lower two-thirds of the jejunum contained altogether about 50 circumscribed areas of hyperplasia infiltration, necrosis, ulceration and hemorrhage. There were several stages to the process. 1. A pigmented raised area five to six mm. without ulceration. 2. The same with much infiltration of periphery. 3. Necrosis. 4. Recent ulceration with fresh blood clotted on the surface of the ulcer (8 mm.). 5. A puckered, pigmented scar 8 mm. in diameter. The mesenteric lymph nodes were not appreciably enlarged. The postperitoneal lymph nodes were enlarged and were similar to the portal nodes. The upper jejunum, duodenum, stomach

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and esophagus were normal. The calvarium was thin and the cranium markedly brachycephalic in type. Brain: Pale, normal. Accessory sinuses; normal. Smears from liver, intestinal ulcers and spleen, contained many histoplasma bodies.

Cause of Death.—Protozoon infection—histoplasmosis.

Histopathology.—Kidney: There was some edema. The epithelium of the convoluted tubules was swollen and in places desquamated and cloudy. Most of the nuclei failed to take the stain. Many of the tubules contained granular débris, desquamated epithelium and occasionally a hyaline cast. There was a slight increase in the intertubular connective tissue and in Bowman's capsule. The space between the glomerulus and Bowman's capsule frequently contained a large amount of coagulated albumin.

Liver: The section showed extensive destruction of the parenchyma by coagulative necrosis having a reticulated character; and the replacement of these areas of necrosis by connective tissue, old and newly formed. The cells of the latter showed an extensive invasion by the micro-organism; many of the cells contained thirty or forty parasites. The process was so extensive that a zonal arrangement could not positively be made out. The older and more extensive areas of necrosis and replacement appeared to be in the portal spaces, where the areas of connective tissue were frequently broader than a liver lobule. The areas of coagulative necrosis varied in size from two or three liver cells up to one-half the diameter of a lobule. These areas of necrosis were scattered everywhere; sometimes isolated, at other times on the margin of a large area, which had apparently undergone necrosis and been replaced by connective tissue. There did not appear to be a shrinkage in this substitutive fibrosis, and there was apparently no distortion of the liver lobule. The areas of necrosis always contained parasites; some parasites appeared to be free, others were enclosed in large vesicular cells, resembling endothelial cells. The heaviest invasion by parasites was in the connective tissue cells, which had replaced the areas of necrosis, and these areas corresponded to the hyaline opalescence noted at autopsy. The connective tissue of the capsule of the liver was thickened and frequently communicated with the infected underlying areas of necroses, but the capsule showed no invasion by parasites. The hepatic vein occasionally was surrounded by connective tissue which had been invaded by parasites. The epithelium of the bile ducts showed no appreciable proliferation and its epithelium was not invaded by parasites.

Ulcer, Ileum: The peritoneum and muscle wall were normal. The mucous membrane was pushed away from the muscle wall by an oval mass of large round and oval cells, most of which had a large amount of eosin-staining cytoplasm, which was more or less replaced by micro-organisms. The periphery of this granuloma, nearest the lumen of the intestine, was denuded of mucous membrane, almost to the depth of the muscularis mucosa. Under the higher power there was seen to be an extraordinary invasion of certain cells in the granuloma by the micro-organism. The nucleus of the invaded cell was either eccentric, or pushed to one side and the micro-organism was closely packed in a clear achromatic space. This achromatic space had no definite membrane and was surrounded by eosin-staining cytoplasm of the cell. Some of the invaded cells did not show this achromatic space, but merely showed a mass of micro-organisms embedded in the cytoplasm of the cell. In this section the blood vessels were not involved, but the lymph spaces everywhere showed an invasion of their lining endothelium by parasites. While most of the micro-organisms were intracellular there was quite a large number apparently free. The epithelium of the tubular glands was everywhere free from an invasion by micro-organisms, yet the interglandular connective tissue stroma and the basement membrane were

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crowded with parasites. The denuded surface of the ulcer was rich in infected cells and there were detached cells and parasites lying free on the surface. The morphology of these free parasites on the surface was the same as those embedded in tissue. Flagella apparently were not present. The cells making up the granuloma were generally large, with small and deeply staining, or large and vesicular nuclei; most of them had a large amount of eosin-staining cytoplasm, while others had a slight affinity for hematoxylin. This section showed a more intense invasion by the parasite than that of any other tissue. Epithelial cells, blood vessels and smooth muscle were not invaded. In this tissue the micro-organisms had spread along the lymph spaces. A peribronchial lymph node showed several large areas in which the lymphoid tissue of the node has been replaced by dense fibrous tissue, in the periphery of which there was a good deal of black pigment. Here and there where the lymphoid tissue still remained there were large cells, sometimes appearing to be a part of the reticulum, at other times endothelial cells bulging out into the lymph spaces, packed with parasites.

Spleen: The splenic spaces were greatly distended by red blood cells and there was a very striking absence of leucocytes in the splenic spaces. The reticulum did not appear to be increased in amount by the proliferation of its elements, but there was an extensive invasion of large cells in the reticulum by parasites, and there was also an invasion of endothelial cells lining the splenic spaces by parasites; on the whole, however, the most extensive invasion was that of cells making up the reticulum of the organ. There was an almost complete disappearance of the lymphoid cells of the Malpighian bodies, the reticulum of which was thickened and fibrous.

Lung: Section of granuloma 2.5 mm. in diameter. The pulmonary alveoli surrounding the granuloma were full of red blood cells. The granuloma consisted of a reticulum conveying small blood vessels. The reticulum was not alveolated but consisted of whorls and strands of loose, connective tissue, small blood vessels, and what appeared to be the remains of alveoli, filled with very large cells, containing micro-organisms. In places there were alveoli partly collapsed, containing very large cells with single or double nuclei; these cells showed an enormous invasion by parasites. Some of the cells must have contained from two hundred to three hundred parasites. The alveoli also contained red blood cells and desquamated epithelial cells, containing both parasites and pigment (dust cells).

PARASITOLOGY.

What is the position of the micro-organism in the zoologic scale? From its morphology, staining characteristics, and the presence of a few flagellated forms, it is regarded as a protozoon having a flagellated phase.

During some microscopic examinations of tropical surface waters, the water was collected in several flasks which were placed on shelves near a window, sealed with paper and cotton to keep dust out, and examined from time to time for the development of flagellates. Most of the flagellates were of the cercomonas type; others had a vibratile short anterior or posterior end near which was located a small refractile dot of chromatin. Opposite was the flagellum, near which was to be found the larger refractile globule of chromatin.

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A sample of water collected July 12, examined August 20, contained a thick surface pellicle having a very disagreeable odor. The pellicle contained numerous radiate colonies of minute cultural forms (*colonies radiées*) and fewer larger oval flagellated forms, having a macronucleus, micronuclear dot, and a short, thin flagellum. Three or four chromatin dots were to be seen occasionally along the periphery of the body. The other samples, collected June 30, examined August 20, contained among other forms an oval non-flagellated body strikingly like the Leishman-Donovan body. Its size was somewhat larger than the Leishman-Donovan body as it is seen in tissues, but the chromatin rod and macronucleus were present. The macronucleus being in the center of the body and the chromatin rod near the periphery between the macronucleus and the pointed end of the body. Between the macronucleus and the broad end of the body was a small oval vacuole.

When these bodies were stained by the intra-vitam method, using gentian violet, or methylene blue, both refractile bodies became stained before the surrounding cytoplasm was tinted. The flagellates remained motile for some time after their centrosomes were stained, then the entire body became spherical and motionless, instead of oviform. These bodies were not cultivable on ordinary laboratory media or in sterilized tap water.

Attempts have so far been unsuccessful in finding in water pellicles a body having the characteristics of *Histoplasma capsulatum.*

In August I learned that Ross,[17] Novy[18] and others had found flagellates parasitic in mosquitoes and fleas. On searching for flagellates in larvæ and adult mosquitoes, I found a few resembling those found in water pellicles.

One larva, *Culex,* three-fourths grown, examined Aug. 30, 1907, contained within a flat-celled body cavity, several oval flagellates with short flagella, having a single refractile dot.

There can be no doubt whatever that protozoa related morphologically to the Leishman-Donovan body can be found in the surface pellicles of tropical waters and in the intestinal tracts of insects, for many of the latter in the larval stages, or in feeding, come into contact with water more or less rich in aerotactic flagellates. The search has been continued for protozoa having a resemblance to the micro-organism described here, by making examinations of most of the animals coming to the laboratory. They include calves, iguanas, raccoons, monkeys, rats, mice, snakes,

17. Ross, R.: Jour. Hyg., 1906, vi, 96, 97, 101-108.
18. Novy, MacNeal and Torrey: Jour. Infec. Dis., 1907, iv, No. 2.

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marsupials, besides various insects. The feces or intestinal tracts are collected, examined and kept for cultivation. The nearest approach to an organism having a morphology resembling that of the *Histoplasma capsulatum* was one seen in some bloody mucus obtained from the inflamed colon of a rat, killed in the laboratory court-yard, April 14, 1908. In this rat protozoon the cytoplasm stains faintly blue. Its outline is round or oval. It contains frequently, two vacuoles, oval in shape, and an open diamond-shaped or irregularly circular granular chromatin ring from which three pair of flagella about twice the length of the micro-organisms are given off, three flagella on each side of the apex of the body. Opposite this, occasionally a single pair of flagella may be seen, similar in length and staining characters to the other pair, viz., eosin-staining and twice the average length of the body. These protozoa are not encysted or encapsulated. Diameter is six microns. They are mildly suggestive of *Histoplasma capsulatum* and very strongly impress one that *Histoplasma capsulatum* has during its flagellate phase several flagella given off from that portion of the body nearest to the clump of chromatin.

SUMMARY.

The clinical notes are very brief, as none of the cases were diagnosed during life.

The most striking clinical features are the splenomegaly, emaciation, irregular remittent temperature and leukopenia.

The patients were men. Two were Martiniquan negroes, the third case was that of a Chinese, who had been a shop-keeper on or near the Isthmus of Panama for fifteen years.

Their local residences were Mariflores, Paraiso and Corozal, small villages on the Pacific slope of the Isthmus, along the line of the Panama Railroad. The Martiniquans were laborers.

Histoplasmosis is not at present encountered. Three cases have entered and died in Ancon Hospital out of thirty-three thousand admissions. This covers a period of about three years.

The greatly improved hygienic condition of laborers throughout the zone has no doubt favored the arrest of the progress of the infection.

Nothing is known about the hygienic condition in which the patients were living.

The cases undoubtedly originated either in Martinique or on the Isthmus of Panama. The Chinese had been living continuously on the Isthmus and at Bocas del Toro, near Colon, for fifteen years.

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It would be difficult to determine the influence of season, as the duration of the disease is not definitely known. Patient 1 died in December at the end of the rainy season; patient 2 died in January at the beginning of the dry season; while patient 3 died in August at the middle of the rainy season.

Postmortem changes were delayed. The body of the Chinese was examined seventeen and one-half hours after death, yet the postmortem changes usually seen in bacterial infections were absent. Subcutaneous tissue was diminished and slightly edematous in case 3. There were numerous subpleural (visceral) ecchymoses in case 1. The ecchymoses corresponded to and overlaid pseudo-granulomata in the underlying parenchyma. There was stellate cicatricial thickening of the pleura over an area of granulomatous tissue in the right lung in Case 3.

In the lungs were disseminated hyaline pseudo-granulomata in Cases 1 and 3. These hyaline areas were round or irregular in shape, pearly white and dense. They were 2 to 3 mm. in diameter when discrete. The irregularly shaped areas were 6 to 12 mm. in diameter. These pseudo-granulomata were always surrounded by raised areas of hemorrhage about 4 mm. wide. There was a terminal bronchopneumonia in Case 2.

The peribronchial lymph nodes, while enlarged and pigmented, did not show the same amount of enlargement noticed in lymph nodes draining the liver and spleen.

The heart was smaller than normal and its size corresponded with the general atrophy of voluntary muscles.

The liver was enlarged in Cases 1 and 3. Case 3 presented a diffuse arborescence, the limbs of the arborescence being about 4 mm. in thickness, having gray centers and yellow peripheries. These areas corresponded to necroses with infiltration by parasites. The capsule was smooth. The portal lymph nodes were enlarged, pale, yellow and friable.

The enlargement of the spleen was marked. The capsule was tense and the pulp firm, yet friable, and dark red. The Malpighian bodies were distinct in Case 1 and indistinct in Case 3. On removal, the spleen was rigid and retained its original form; it was not flexuous. The lymph nodes draining the spleen were similar to those draining the liver.

The pancreas, bladder, ureters and genitalia were negative.

The ileum, jejunum and colon were the seats of a process that appeared first as a circular raised pigmented granuloma in the mucosa. The infiltration increased at the periphery and later a small circular ulcer appeared, 8 mm. in diameter. Still later a pigmented puckered scar was noted. One of the ulcers in Case 3 was covered with recent blood.

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The duodenum, upper jejunum, stomach and esophagus were normal.

The mesenteric lymph nodes were not appreciably enlarged.

The postperitoneal lymph nodes were enlarged, pale and friable.

The peritoneum covering the rectum, sigmoid flexure and the parietal peritoneum near Poupart's ligament was intensely pigmented black in spots.

The brain and rib marrow were negative, and the accessory nasal sinuses normal.

The micro-organism was found in endothelial cells lining blood and lymph vessels and in areas of necrosis and pseudo-granulomata, in the intestinal tract, spleen, liver, lungs, lymph nodes and rib marrow.

The bodies are round and oval. There is among the larger forms a tendency toward an oval outline. An average-sized spherical body is 3 microns in diameter. The longer diameter of an oval body is 3.75 microns. The bodies are always surrounded by a clear, refractile, achromatic zone or capsule, giving the impression at once of an encysted protozoon. The body does not stain hemogeneously, but very irregularly, hardly any two parasites looking exactly alike. The body consists of a deeply staining substance, or chromatin, a faintly staining substance staining light blue with polychrome stains; and achromatic spaces. The deeply staining substance, or chromatin, is practically always heaped up along one side or end of the body; sometimes it consists of a single mass or several small masses of chromatin; sometimes it is ring-shaped or occasionally extending along half of the periphery of the body, being crescent-shaped. Occasionally a chromatin dot or very rarely a chromatin rod will be seen near the larger chromatin body. This chromatin dot or chromatin rod may sometimes be at the opposite end or side of the body. There may be several such dots of chromatin. When there are several of good size the bodies appear to be in a presegmenting stage. The faintly staining blue substance takes up the rest of the space, excepting where there may be one or two small achromatic zones, resembling the vacuoles of protozoa. These vacuoles are irregularly disposed, being sometimes in the center and at other times near the periphery of the body. The most striking thing about the parasite is the extremely irregular way in which the staining substance is disposed. This is in striking contrast with the appearance of the Leishman-Donovan body.

The micro-organism is a protozoon probably belonging to the *Flagellidia* and is probably related morphologically to small oval protozoa having several pairs of flagella in relation with the large chromatin mass.

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This latter is suggested on account of certain morphologic analogies. Of course, it will be necessary to cultivate the micro-organism from splenic pulp obtained from a patient during life in order to determine its morphology in the flagellated stage.

The parasite always takes polychrome blue stains like a living organism. Twenty-four hours after the death of the host, the chromatin and faintly staining basophilic substance of the micro-organism stains beautifully. Under similar conditions the malarial parasite would not stain so well. Occasionally in marrow smears the micro-organism requires prolonged contact with the stain, probably due to the resistance or impermeability of the refractile capsule. The portal of entry is unknown. The disease may be transmitted by a suctorial insect or acarid, or the micro-organism may gain entrance to the tissues of the host through the intestinal tract.

Case 3 presented several cutaneous papules; Cases 1 and 3, small intestinal ulcers and granulomata. The intense invasion of the spleen and liver, of the lymph nodes draining these, and the presence of intestinal lesions, is strongly suggestive of an entrance through the intestinal tract —ileum or colon.

Cases 1 and 3 presented infected pulmonary pseudo-granulomata, while Case 2, which did not present so intense a general infection, showed no pulmonary pseudo-granulomata. The pulmonary lesions, therefore, may appear late. The micro-organism differs from the Leishman-Donovan body in having a more complex arrangement of its deeply staining substances or chromatin, of a lack of uniformity to the disposition of the chromatin and in not possessing a chromatin rod.

The disease caused by the micro-organism must be like kala-azar because of the corresponding splenomegaly, emaciation, irregular pyrexia and leukopenia.

The chief anatomic difference is the pseudo-granuloma in the lungs. I have found no reference to such a lesion in the records of East Indian autopsies.

In conclusion it should be said that this disease, although no longer seen in Panama, is probably to be found in unhygienic and less salubrious regions of tropical America, not yet disturbed by the sanitarian

Up to the present, *Histoplasma capsulatum* has not been found in smears or sections of localized skin ulcers or granulomata. Reasoning from analogy it will be found, if not in Panama then in some other region of tropical or subtropical America. The researches of Captain

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James,[19] I.M.S., show that the geographical distributions of kala-azar, the general infection by the Leishman-Donovan body, and of Delhi or Oriental sore, the localized infection, are not the same. Oriental sore is common in Bagdad and the Punjab, the latitude of the former being about that of Charleston, S. C., or southern California, while kala-azar is endemic in Assam and Madras.

I wish to express my thanks to Colonel W. C. Gorgas, U.S.A., Chief Sanitary Officer, and to Major John L. Phillips, U.S.A., Superintendent of Ancon Hospital, for their kind permission to publish this report.

Ancon Hospital.

DISCUSSION.

DR. H. B. WARD, Lincoln, Neb.: Speaking from the zoologic standpoint, I can hardly support the apparent conclusions of Dr. Darling with regard to the affinities and source of the organism. It seems to me in the highest degree unlikely, from what we know of parasitic organisms heretofore, that the making of chance cultures from water would be likely to secure the same organism. So far as these organisms have been worked out in India they show distinctly a stage which is resident in one host and a stage of transmission. There is great difference of opinion as to whether the transmitting agent is a necessary link in the life of the host or merely a mechanical vector. But all the evidence on the Leishman-Donovan body shows that it does not have an external stage, and Captain Patten, in his lectures, emphasized, from direct and indirect evidence, the great improbability that there can be an external or free living stage of the organism. I then suggest the improbability that the organism which Dr. Darling has found under very similar biologic conditions to those of the Leishman-Donovan body, could of itself be found in nature free. So far as the evidence presented goes it does not seem to show conclusively that this organism should be relegated to the flagellata. The presence of occasional flagellates does not show any necessary connection with the bodies which were found in the epithelial cells. Hence there is still a possibility that the organism which has been described belongs to some other group of protozoa. So long as we know positively only the asexual phase of any protozoon we are entirely at a loss to know where it should be placed. The asexual phase of a number of types in various groups of protozoa is so similar that the mere microscopic examination will not in any way suffice to distinguish them. The basis of distinction must rest on the character of the sexual phase and sometimes on the working out of the entire life history. This comment is not intended as a criticism of the paper as a whole, but merely to call attention to the danger of conclusions with reference to the supposed source of the parasite as being the evident means of infection. In numerous cases investigation of similar subjects has been led far astray by too great insistence on a possible origin of the pathogenic organism.

DR. SAMUEL T. DARLING, Ancon, Panama: If there had been time to read all of the paper, perhaps it would have been made clear that my statement about this protozoon being placed with the flagellidia was based on morphology and staining characteristics. It is true that morphology does not form the best basis for the classification of protozoa, but the living protozoon in these three cases

19. James, S. P.: Scientific Mem. by Officers of the Medical and Sanitary Departments of the Government of India, Calcutta, 1905, new series, No. 13.

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was not studied. Cultural experiments could not be carried out because the clinicians failed to discover the condition in the wards while the patients were living, and when cultures from splenic pulp might have been made. I realize that there were few flagellated bodies seen in smears, but it was also from the resemblance in staining characteristics to other protozoa that led me to think that this protozoon was probably related to the flagellidia. Referring to the Leishman-Donovan body having an extracorporeal cycle, I understand from Rogers' recently published work on tropical fevers, and from Captain Patton's communications, that it was Rogers himself who first suggested the bedbug as being the intermediate host for the Leishman-Donovan body. It is true that the making of chance cultures is not the quickest or the most logical way of determining the zoologic status of *Histoplasma capsulatum*. I was simply trying to find protozoa resembling the one discovered by me in man. It was not unlike the method successfully pursued by Ronald Ross in his search for the intermediate host of the malarial parasite.

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A CLINICAL AND PATHOLOGIC STUDY OF A CASE OF ADAMS-STOKES' DISEASE.*

HARVEY G. BECK, M.D.
AND
WILLIAM ROYAL STOKES, M.D.
BALTIMORE.

This disease, which was first described by Adams[1] in 1827, did not receive general recognition until 1846; at this time Stokes[2] published his studies of the subject and presented a more complete clinical picture. After this it was known as Adams-Stokes' syndrome. In the past few years, since the pathology has been more definitely determined, it is usually described as Adams-Stokes' disease.

The disease is perhaps not as rare as one is led to believe in looking over the literature. Michael and Beutlemiller[3] were able to collect about seventy cases, the majority of which were reported in the last few years. The fact that cases are more frequently reported in recent years is due to the great interest aroused by the discovery by His of the auriculoventricular bundle and to the studies of the physiologic function of this bundle by Erlanger.

While we do not feel it necessary to report our case to help prove the correctness of the relation existing between disease of the bundle and the symptoms of Adams-Stokes' disease, we do feel justified in presenting it because it is a unique case in so far as the character of the pathologic lesion is concerned, and, therefore, adds at least something of interest to the subject.

Before Gaskell, His, Jr., Tigerstedt and Erlanger demonstrated, by ingenious experiments, that the symptoms of Adams-Stokes' disease and those of heart-block were practically identical, numerous theories were advanced as to the cause of this condition. Stokes himself approached

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* This article is illustrated from negatives which were made in color by the Lumière process direct from the specimens.

1. Adams: Dublin Hosp. Rep., 1827, iv, 396.
2. Stokes: Dublin Quart. Jour. Med. Sc., 1846, ii, 73.
3. Michael and Beutlemiller: Berl. klin. Wchnschr., Nov. 18, 1907, xliv, 1474.

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more closely to the true nature of the underlying pathologic basis when he suggested that the lesion was in the heart muscle. Charcot suggested that the lesion was in the medulla. Houchard[4] held that there was present a disease of the cerebral vessels associated with a disturbance of the mechanism of the heart.

Gibson[5] and Jacquet[6] recognized the presence of heart-block, and thought that there was a similarity with intermittent claudication. By others it was recognized as fatty degeneration of the heart muscle and tumors of the vagus, or pressure on the vagus. In spite of the fact that the results of the recent investigations by His, Jr., and his coworkers seem so conclusive, there still appears to be some disparity in opinion as to the cause of this disease. Thus Pearson[7] holds that the existing cause resides at different levels of the nervous mechanism.

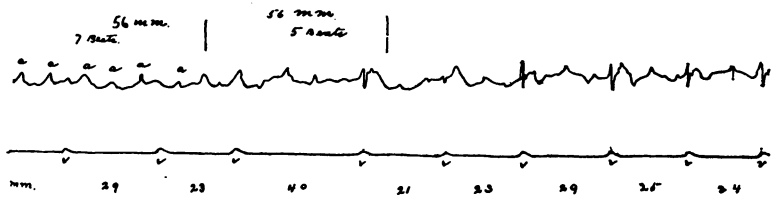

Fig. 1.—Pulse tracing of patient described in case history; *a*, auricular pulse; *v*, ventricular pulse. Lower figures represent the difference between each ventricular pulse in mm.

The many interesting studies on the physiology of the heart, especially those relating to the cause of its rhythmic action, all tend to confirm the view of those who favor the theory of the myogenic origin of the condition and tend to disprove the neurogenic theory. It has been demonstrated that the inherent rhythmicity is not dependent on the nervous mechanism, although it has a governing influence over it. In favor of this view may be mentioned the fact that, in the fetal heart, contractions occur before the nervous system is developed.

In the myogenic theory, it is assumed that the impulse passes from the auricle to the ventricle and that there is a brief interval between the contraction of the auricle and the contraction of the ventricle. In the mammalian heart, it has been found that by warming or cooling the area between the mouths of the two venæ cavæ, the heart-rate can be modi-

4. Houchard: Traité des maladies du cœur.
5. Gibson: The Nervous Affections of the Heart, 1904, p. 65.
6. Jacquet: Deutsch. Arch. f. klin. Med., lxxii, No. 2.
7. Pearson: Dublin Jour. Med. Sc., October, 1907.

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fied,[8] and as this is the only area which influences the whole heart's action[9] it is safe to assume that the impulse begins at this point and passes through the auricle into the ventricle. The assumption that this impulse is conducted through the muscular fibers led to the natural inference that there must be a connective bundle between the auricle and the ventricle.

In 1893 His, Jr.,[10] described a muscular bundle connecting the auricle and ventricle through the auriculoventricular septum. Little attention was paid to the discovery of His until 1904, when Retzer,[11] Brauning,[12] and Humblet[13] confirmed His' observations and gave a complete description of the anatomy of the bundle of His.

A number of observers have contributed articles on the dissociation of the auricles and ventricles. Stannius,[14] in 1852, first observed this phenomenon in cold-blooded hearts after ligation of the sinoauricular junction. The results obtained experimentally by this method are fully described by Gaskell,[15] who succeeded in producing independent auricular and ventricular contractions in the heart of a tortoise by constricting the circular layer of the muscles at the auriculoventricular junction. Wooldridge,[16] in the same year, was able to sever the functional connection between auricles and ventricles by crushing the tissue in the auriculoventricular junction. This had the effect of producing an independent rhythm for both auricle and ventricle and a marked slowing of the ventricles. His, Jr.,[17] in 1905, demonstrated the same condition by simply destroying the auriculoventricular bundles.

In 1905 Hering confirmed His' experiments. At the same time Erlanger was performing his valuable experiments, but using different methods. Erlanger's results are best described in his own words:

With gradual compression of this bundle, the following phenomena may be noted: First may be seen a slight increase in the interval between the beginning of an auricular and the beginning of its independent ventricular contraction. This, then, is the first sign of heart-block. With further clamping, a degree of

8. McWilliam: The Rhythm of the Mammalian Heart, Jour. Physiol., 1888, ix, 167.
9. Adam: Pfluger's Arch., 1906, cxi, 607.
10. His, Jr.: Arb. an d. med. klin. zu Leipzig, 1893, p. 14; Centralbl. f. Physiol., 1895, ix, 469.
11. Retzer: Ueber die musculose Verbinding zwichen Vorhof und Ventrikel des Saugethierherzens, Arch. f. u. Entwcklngsgesch., anat. part, 1904, p. 1.
12. Brauning: Arch. f. Physiol., 1904, supplement, 1.
13. Humblet: Arch. internat. de physiol., 1904, vii, 278.
14. Stannius: Arch. f. Anat., Physiol. u. wissensch. Med., 1852, p. 87.
15. Gaskell: Jour. Physiol., 1883, iv, 43.
16. Wooldridge: Arch. f. Physiol., 1883, p. 552.
17. His, Jr.: Centralbl. f. Physiol., 1895, ix, 469.

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Fig. 2.—The color photograph of the heart shows the heart laid open, exposing the endocardium of the left ventricular septum. The calcareous nodule at the base of the segment of the mitral valve is well shown and in the cross section of the muscle of the left ventricle a calcareous nodule is seen just below the base of one of the cusps of the aortic valve. (Prof. W. T. Simon.)

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compression may be reached in which this interval, the intersystolic period, gradually increases in length with successive beats until eventually the ventricles fail to respond to one of the auricular impulses. Following this ventricular silence, the intersystolic period is short, but it immediately begins to lengthen again until another ventricular beat is dropped. In this way states may be produced in which ventricular beats may be dropped quite regularly in 10, 9 or 8, etc., auricular beats. With further clamping, more advanced stages of partial block may be obtained, stages in which only every other or every third or every fourth auricular beat may stimulate the ventricles, giving rise to what are generally termed 2:1, 3:1, 4:1, etc., rhythms, respectively. The ventricles may beat independently of the auricles, although the block is not actually complete. This state has been termed relative complete block. Finally, when the pressure on the auriculoventricular bundle becomes such that the auricular impulse fails to pass the obstruction, the block becomes absolutely complete. In both forms of complete block, the ventricles beat more slowly than the auricles, and independently of them. This state of affairs is seen in advanced stages of Adams-Stokes' disease.

In relative or partial heart-block, the rhythm of the ventricles is influenced by the rate of the auricular contractions. Experiments seem to demonstrate what is borne out by clinical observations (Fig. 1) that the auricular impulse is inverse to the auricular rate. Therefore, when the auricles beat rapidly, the impulses are not of sufficient strength to stimulate the ventricles to contraction, and the rhythm which becomes more complete may change from 2:1 to 3:1 to 4:1, etc., or even complete block may ensue. In this connection it is interesting to mention the effect of stimulation of the vagus and accelerator nerves in both partial and complete block.

Both the vagi and accelerators have very slight influence on the rate of the ventricles during complete block, but the auricles are affected as usual.

Usually, at the moment when partial block passes into complete block, the ventricles cease to beat altogether, until they are stimulated to an independent action by their inherent rhythmicity. It is at this stage of Adams-Stokes' disease that the syncopal attacks develop, and these attacks are invariably associated with the so-called stoppage of the ventricles. Erlanger and Hirschfelder[18] made a series of experiments with the object of studying the phenomenon of stoppage of the ventricles and its relation to the syncopal attacks of Adams-Stokes' disease. The results of these experiments were overwhelmingly in favor of the view that "the ventricles cease to beat for a time, when they are no longer whipped into action by their physiologic stimulus, because some time is required for

18. Erlanger and Hirschfelder: Further Studies on the Physiology of Heart-Blocks in Mammals, Am. Jour. Physiol., 1906, xv, 153. Hering, H. G.: Arch. f. d. ges. Physiol., 1905, cvii, 97.

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the dormant inherent rhythmicity of the ventricles to acquire its maximum efficiency." Erlanger and Hirschfelder were inclined to believe that the syncopal attacks result from the sudden cessation of the influence of the auricles over the ventricles. They observed that in one of their cases the ventricular stoppage was always preceded by an acceleration of the auricles. This also occurred in our case.

CLINICAL OBSERVATIONS.

Patient.—A man, aged 72, with a splendid family history. With the exception of malaria from the age of 14 to 40 years, while residing in Virginia, and two attacks of pneumonia between 50 and 60 years of age, the patient had enjoyed remarkably good health. His occupation was blacksmithing and steel inspecting, which he followed actively until the summer of 1907. He was an inveterate smoker for years, and occasionally took a glass of beer; otherwise his habits were most exemplary.

Onset of Symptoms.—This dates from an injury which he sustained July 9, 1907. In crossing the railroad, he stepped underneath the gate which was being lowered, and received a slight blow on the head. He fell and was unconscious for one or two minutes, after which he was able to walk unaided. Four days later a sensory aphasia suddenly developed. This was associated with a slight weakness of the right arm. There were no other evidences of paralysis. The patient remained in bed for several weeks, although he was able to walk. His pulse at this time ranged from 60 to 64, but there was no disturbance of rhythm noted. The aphasia began to subside after one week, and it gradually improved until only a slight hesitancy in speech remained. In a month he was going about freely and doing light work. In the latter part of November he began to have "weak spells," in which he fell, but did not become unconscious. These attacks lasted only a few moments. He was in the habit of walking close to buildings or fences, in order to support himself when an attack came on and prevent himself from falling. The family had noticed that during his sleep he had been breathing irregularly (Cheyne-Stokes) for some time. On Jan. 4, 1908, he was taken with a series of attacks (probably ten within an hour and a half) which we had the opportunity to study. These attacks recurred frequently, although at very irregular periods for the next two weeks, after which occasional attacks developed until they finally disappeared entirely.

Physical Examination.—The patient was a tall, slender, fairly well-nourished individual and appeared much younger than his actual age. The color of the skin and mucous membrane was normal. There was no inequality in the size of the pupils and both reacted promptly to light and accommodation. Arcus senilis was present, but not marked. An epithelioma, the base of which was about the size of a dime, was situated on the right cheek over the malar bone. The tongue was clean and not tremulous. The chest was fairly well developed, and expansion was equal on the two sides. Pulmonary resonance was good and breath sounds were normal. In the recumbent posture, the cardiac impulse at the apex appeared in the fifth intercostal space, directly inside the nipple line. It was slightly diffused, but not heaving in character. No thrill was present. Marked irregular pulsations were constantly seen in the veins, at the base of the neck, averaging from 76 to 90 per minute. The radial pulse was slow, ranging from 26 to 32 per minute, and the tension was minus. The rhythm was not much disturbed, except on those days when the patient suffered with frequent syncopal attacks. The condition of the arterial walls was about normal for a man of the patient's age. The area of cardiac dulness was somewhat increased

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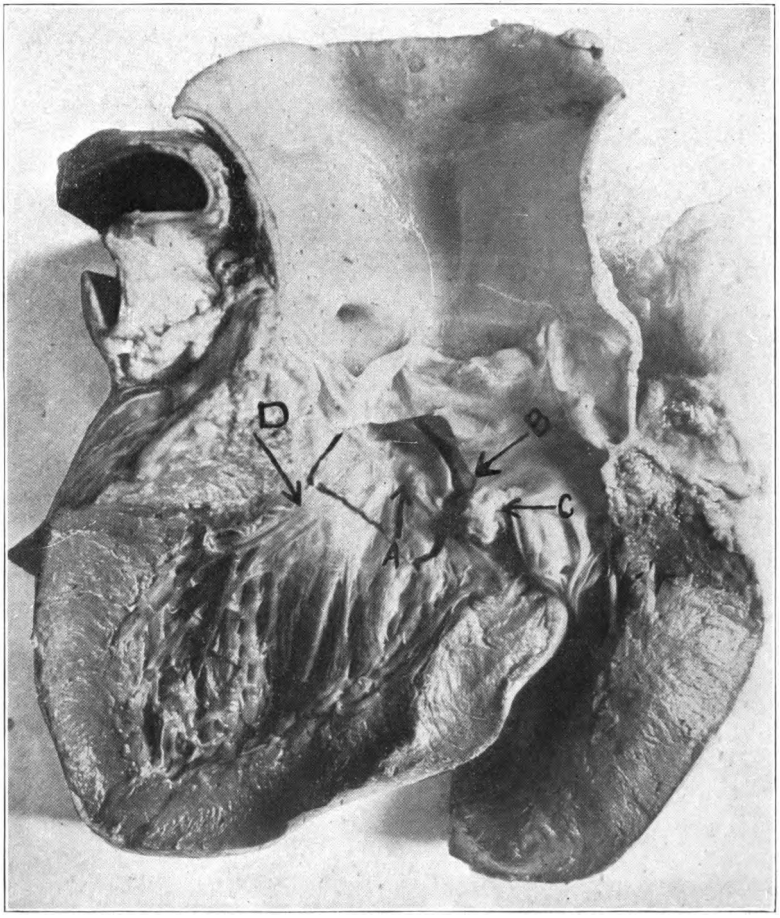

Fig. 3.—This shows a photograph of the gross specimen and at C the large irregular calcareous nodule is seen. B indicates the calcareous area just in the region of the bundle of His, as it comes from the auricle, and A shows the irregular calcareous column beneath the endocardium which pressed upon the bundle of His in its course between the fibrous ring and the ventricular septum. D shows the branching of the bundle just beneath the endocardium of the left ventricle. (Dr. T. M. Wright.)

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in the transverse diameter, more to the right than to the left. No definite murmurs were heard. At the apex, the first sound was feeble, the second was clear and more distinct. Between each ventricular systole were heard faint, short and somewhat indistinct sounds. Their maximum point of intensity was toward the base of the heart, diminishing toward the apex, and lost entirely at the mitral area. There was no evidence of gastrointestinal disease. Liver dulness was normal; the spleen was not palpable and the urine was negative.

Character of Attacks.—The character of the attacks did not vary much, except in degree. Some were apparently much more severe than others. They were usually preceded by a distinct aura, which was in the form of sounds resembling the ringing of bells or music. This was associated with intense pain in the right side of the head and face. There was also spasmodic contractions of the muscles in this area. During this stage the patient raised up in bed, grasped the right side of the face with the right hand and groaned. He soon afterward sank into unconsciousness, which lasted from five to fifteen seconds. During this period the color of the face was an ashen gray; the lips were cyanotic and the breath was slow, irregular and stertorous. After returning to consciousness, he sank his head into the pillow and lay exhausted, with beads of perspiration on the face and extremities. In all the earlier attacks and the minor attacks during the course of the disease, unconsciousness was not complete and the other symptoms were not as marked. We are indebted to Dr. Arthur D. Hirschfelder, who saw the patient with us several times and took some interesting pulse tracings. The one reproduced (Fig. 1) in this article was taken Jan. 12, 1908, one week after the onset of this series of attacks. While Dr. Hirschfelder was taking tracings that day, the patient had several seizures with syncope and convulsive movements. The accompanying record was taken shortly after these attacks and shows a brief stoppage of the ventricles without any other associated phenomena. The tracing shows distinctly the acceleration of the auricular beat with a diminished contraction, a condition which usually precedes a ventricular pause. During the stage in which the auricular impulse was feeble, the ventricles contracted independently of the auricles, causing complete heart-block. Finally, when the auricular rhythm became more regular and the force of the contraction stronger, it will be observed that every other beat stimulates the ventricles to contraction, thus producing a 2:1 rhythm.

Subsequent Course.—After the syncopal attacks subsided, the ventricles continued to beat independently, and the patient enjoyed comparative comfort. The pulse ranging from 28 to 30 per minute, remained fairly regular, and was influenced by change of position. The patient died suddenly in bed March 5, 1908.

PATHOLOGIC STUDY.

THE ANATOMY OF THE BUNDLE OF HIS.

The anatomy of the bundle of His is carefully described by Retzer.[11] The old ideas were based on the neurogenic theory. This theory taught that the impulse of contraction came from the auricle to the ventricle and was transmitted by nerves. This was not proved by experimental work, and the later myogenic theory has been confirmed by the painstaking work of His and Retzer.

Retzer states that the myogenic theory depends primarily on the demonstration of a constant muscle connection between the auricle and ventricle. The exact position should also be shown, and it should be

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found in the lower class of animals as in the later stage of development of the human embryo.

Gaskell showed a connection between the muscle of the auricle and ventricle of the tortoise. He found a circle of muscle fibers in the fibrous ring between the auricle and the ventricle from which auricular and ventricular fibers had their origin. Kent[19] also described a muscular connection between the auricle and ventricle in such mammals as rats and rabbits.

Wilhelm His, Jr., described the auriculoventricular bundle as follows: "The muscular bundle springs from the posterior wall of the right auricle near the auricular septum in the auriculoventricular groove; it lies in the upper margin of the muscular septum of this chamber and passes forward through this until near the aorta. It then divides into a right and left limb, and the latter ends at the base of the aortic cusp.

Retzner, in a most painstaking research, has confirmed the findings of His in the main, and his examinations include the microscopic study of the hearts of cats, rabbits, rats, dogs and human beings.

Sections were cut perpendicular to the ventricular septum and parallel to the heart's axis and passing through the ventricular septum and the auricular border. Retzer was always able to demonstrate the cross-section of a muscular bundle that was sharply limited from its surroundings by connective tissue. This contrast was best brought out by Van Giesen's or Mallory's connective-tissue stain. This cross-section of what we may now call the bundle of His is found at the upper end of the septum ventriculorum directly beneath the membranous part of the septum. From the point where the bundle extends backward into the auricle, the connective tissue becomes scarcer and at last disappears, and the bundle can be no longer distinguished from the other muscle structure. From the point where the muscle is found in cross-section it also courses forward in the septum and divides into a right and left branch which send out fibers into the general muscular structure of the right and left ventricle.

On a sagittal section of the septum the bundle appears lengthwise, and the membranous portion stains blue by Mallory's stain, while beneath this the bundle of His can be seen. This bundle is not so compact as the rest of the heart muscle and contains more connective tissue. Retzer was unable to find any other muscular connection between auricles and ventricles in the auricular groove, and he thinks that he was able to exclude the presence of any other large bundle as a muscular connection.

19. Kent: Jour. Physiol., ix, 167.

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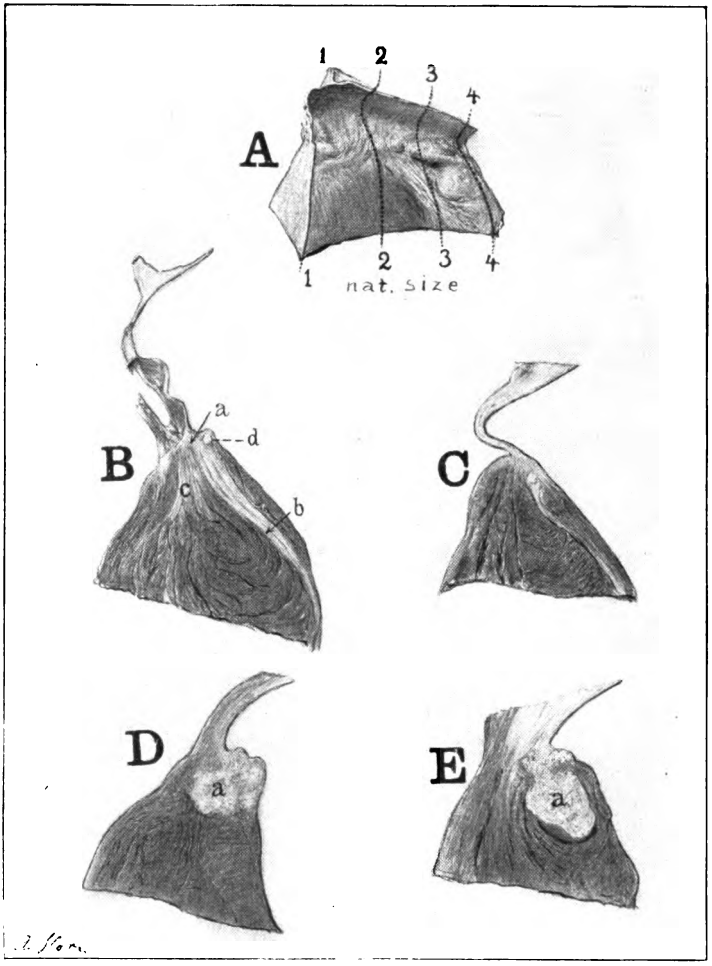

Fig. 4.—This shows a drawing of the block of heart muscle involving the ventricular septum and the fibrous auriculoventricular septum. A shows the calcareous nodule directly in the course of the bundle of His. B (which is Section 1, 1, in A) shows the branching of the bundle for the right and left ventricle; (a) indicates the position of the bundle of His in cross section between the fibrous auriculoventricular ring and the muscular portion of the ventricular septum; (b) indicates the branch for the left ventricle; (d) a calcareous nodule just above this branch; and (c), the branch for the right ventricle. C (which is Section 2, 2, in A) shows a small calcareous nodule just below the bundle of His. In D (which is Section 3, 3, in A) at (a) the irregular calcareous mass is seen to involve most of the area of the bundle of His, and in E (which is Section 4, 4, in A) at (a) the nodule is seen projecting into the region occupied by the bundle of His. (Mr. A. Horn.)

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By means of a lucky accident Retzer was able to demonstrate the gross anatomy of the bundle of His in the human heart. In an attempt to macerate the specimen the connective tissue of the auriculoventricular septum became so soft that the auricle separated from the ventricle and they only remained connected by the thin bundle of His.

This bundle, when viewed macroscopically from the left side of the heart, lies directly above the muscular septum of the ventricle and underneath the membranous portion of the septum. This bundle can often be seen as a delicate strand if the septum is held to the light. The bundle can be traced backward only to the right fibrous trigonum, but forward one can trace the bundle into the muscle of the ventricles. On the right side of the heart the bundle lies under the medial leaflet of the tricuspid valve, and this valve must be cut away in order that the bundle may be seen, and the endocardium must also be dissected from the auricles to the septum. After removing the muscular portion of the septum the bundle is then seen in the auriculoventricular junction where it spreads out into the musculature of the right auricle.

It may be seen, therefore, as fibers arising in the right auricle passing backward immediately above the interventricular septum, bifurcating into a right and left branch which pass down to their respective sides of the ventricle.

PATHOLOGY OF THE BUNDLE OF HIS.

Sendler,[20] in 1892, reported a case of a woman, 35 years old, who suffered for six months with fainting spells and slow pulse ranging in frequency from 24 to 37. The autopsy showed an enlarged heart. In the right ventricle 1 cm. underneath the opening of the pulmonary artery, but not involving the valve, there was a fibroma the size of a walnut. Although no microscopic sections were made, it seems that the tumor must have involved the bundle of His and produced the symptoms mentioned above.

In 1905 a case of Adams-Stokes' disease was reported by Stengel,[21] in which an atheromatous mass was found on the anterior leaflet of the mitral valve toward the base. He stated that it was over the bundle of His, where it passed from the auricle to the ventricle, but no microscopic studies were made at that time.

Schmoll[22] also described a case of Adams-Stokes' disease in which there were three or four auricular contractions to one ventricular beat.

20. Sendler: Centralbl. f. klin. Med., 1902, p. 642.
21. Stengel: Am. Jour. Med. Sc., 1905, cxxx, 1083.
22. Schmoll: Jour. Am. Med. Assn., Feb. 3, 1906, xlvi, 361.

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No macroscopic evidence of any lesions was detected, but microscopic study showed scar-formation in and around the bundle of His.

Jellick, Cooper and Ophüls[23] also reported a case of gonorrheal epididymitis in which the symptoms of Adams-Stokes' disease appeared two weeks before the patient's death. The autopsy showed an infarction in the region of the bundle of His, caused by thrombosis of the arteries, and Cooper[24] cited a case in which lesions were found in the bundle of His. Butler[25] described a similar case in which the bundle of His was infiltrated by fat to such an extent that it was atrophied to one-fifth its natural size.

Dr. Heineke[26] showed a heart at the Medical Association of Munich, June 12, 1907, from a case of Adams-Stokes' disease from which star-like gummatous myocarditis was found in the position of the bundle of His.

Hay and Moore[27] described a typical Adams-Stokes' syndrome lasting for several years in which the necropsy showed rigid and calcified coronary arteries, the right artery being almost occluded and both auricles and ventricles hypertrophied and dilated. The aorta contained a few atheromatous patches. The microscopic examination of the bundle of His showed that the central fibrous body of the bundle was an atheromatous mass, and portions of the bundle were infiltrated by many fibroblasts showing a chronic inflammation of a patchy character.

Grunbaum[28] also found a gumma in this bundle, causing typical symptoms.

Ashton, Norris and Lavenson[29] have reported a most interesting case of Adams-Stokes' disease with a complete microscopic study of the sections obtained at the autopsy. This patient had all the cardinal symptoms, including the attacks of vertigo with unconsciousness, bradycardia and incoordination of the auricles and ventricles. After numerous attacks occurring at intervals during one month the patient died, and autopsy showed a slightly hypertrophied heart, chronic passive congestion of the viscera, and a gumma of the heart involving the bundle of His. This large gummatous mass was found directly below the posterior

23. Jellick, Cooper and Ophüls: Jour. Am. Med. Assn., March 31, 1906, xlvi, 955.
24. Cooper: Jour. Am. Med. Assn., July 28, 1906, xlvii, 302.
25. Butler: Am. Jour. Med. Sc., May, 1907.
26. Heineke: Berl. klin. Wchnschr., Sept. 2, 1907, p. 1125.
27. Hay and Moore: Lancet, London, Nov. 10, 1906, clxxi, 1271.
28. Grunbaum: Progr. Med., September, 1906, p. 75.
29. Ashton, Norris and Lavenson: Am. Jour. Med. Sc., January, 1907, cxxxii, 28.

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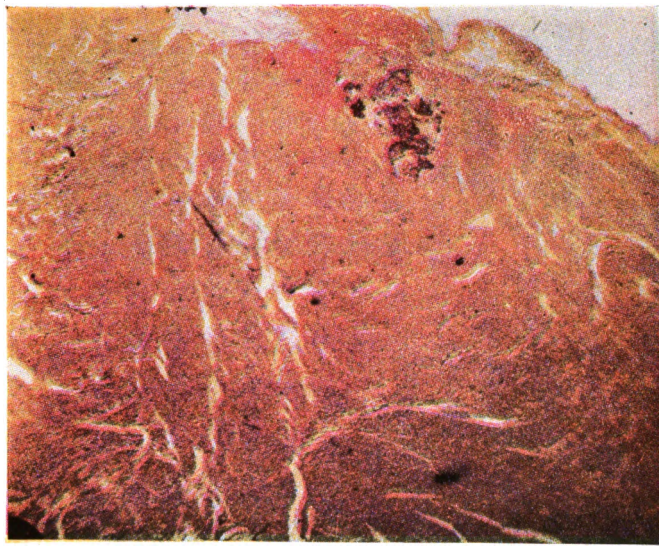

Fig. 5.—This is a color photograph of a cross section of the bundle of His which is shown at the upper part of the picture, just below the red connective tissue of the fibrous ring. To the right of this bundle and separated from it by red connective tissue is a small calcareous nodule, and running through the entire center of the picture is the longitudinal section of the branch of the bundle of His for the right ventricle. The small branch for the left ventricle is also seen beginning to the right of the calcareous nodule. These sections were made from Segment B, Figure 4, Van Giesen's connective tissue stain. (Dr. T. M. Wright.)

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aortic cusp and passed entirely through the uppermost portion of the interventricular septum causing a projecting mass in the right ventricles, just beneath the middle tricuspid leaflet. It will thus be seen that this gumma passed completely through the area occupied by the auriculo-ventricular bundle. Sections through the ventricular septum perpendicular to the long axis of the heart showed that the bundle of His was completely cut in two by the gummatous process, just after the bundle left the interauricular septum and entered the ventricular septum below its membraneous or fibrous portion.

Fahr[30] has reported two cases of Adams-Stokes' disease. In one of his cases he found a mass of connective tissue forming a scar which completely cut through the left branch of the bundle of His just as it divides in order to run in the upper layers of the left ventricle. In the other case the microscopic examination revealed a gumma just as it makes its exit from the annulus fibrosus between the auricles and ventricles.

AUTOPSY REPORTS.

HEART MEASUREMENTS.

An autopsy was made about two hours after death, but the heart was the only organ that could be removed. The liver and lungs showed no evidence of chronic passive congestion. The heart on removal was found slightly enlarged, weighing 450 grams. Measurements:

1. Just above the aortic valve, 8.5 cm.
2. Length of left ventricle, including muscle, 8.5 cm.
3. Thickness of left ventricle midway, 21 mm.
4. Mitral valve, 10 cm.
5. Pulmonary valve, 8 cm.
6. Length of right ventricle, 10 cm.
7. Thickness of right ventricle, 6 cm.
8. Tricuspid valve stretched, 14 cm.

NEW GROWTHS WITHIN THE HEART.

On opening up the left side of the heart, a calcareous projecting nodule was found, measuring about 9 mm. in diameter and extending from 6 to 9 mm. out into the chamber of the ventricle. The mass was somewhat irregular in shape and of a yellow color. It was about 2 cm. immediately below the mesial aortic cusp and ran backward along the upper portion of the ventricular septum, following the course of the coronary artery and involving also the attachment of the anterior leaflet of the mitral valve. An irregular projection of this mass also passed through just beneath the endocardium in a position corresponding to the junction of the muscular portion of the ventricular septum with the membranous portion of the septum. This mass projected forward in the upper portion of the septum for a distance of 12 mm. from the base of the original calcareous mass and occupied therefore the position of a portion of the bundle of His as it passed through the ventricular septum before dividing into the branches for the left and right ventricles. This mass, therefore, extended for about 1 cm. in the position of the bundle of His and ended about where the bundle divided

30. Fahr: Virchow's Arch. f. Path. Anat., 1907, clxxxviii, 562.

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into its two ventricular branches. It must have interrupted the impulse from the auricles to the ventricles conveyed through the bundle of His.

There was another smaller calcareous nodule just at the posterior aortic cusp. This cusp was slightly shrunken and calcareous and there are a few atheromatous patches in the aorta.

CORONARY ARTERIES.

The transverse branch of the left coronary artery was completely calcareous; for a distance of 4.5 cm. it forms a rigid tube, but its lumen was not completely obliterated as it admitted a probe of a little less than 1 mm. in diameter.

The descending branch was not completely calcareous, but it was thickened and comparatively rigid for a distance of 3.5 cm. as it descended to the apex. It would also allow the passage of the probe mentioned above.

About 4 cm. from the origin of the aorta the right coronary artery was firm, bony and rigid for a distance of 1.8 cm. This ended just as it divides into the descending and transverse branch and the transverse branch continued as a thickened tube, while the descending branch was very tortuous.

The main branch of the right coronary artery from its origin to the rigid portion was simply thickened. The color photograph, or Figure 2, shows the calcareous mass projecting from the base of the mitral valve, projections from which invaded the area of the bundle of His.

MICROSCOPIC EXAMINATION.

For the purpose of microscopic examination a block of the heart tissue was cut from the specimen which involved practically the entire course of the bundle of His through and beneath the auriculoventricular septum, which also included its branches for the left and right ventricles.

The photograph seen in Figure 3 will show this block of tissue as viewed from the left ventricle. In this plane it is seen to include the endocardium covering the left ventricle at the extreme upper portion of the ventricular septum and also the annulus fibrosus or auriculoventricular fibrous ring above.

This block was divided into three portions, which are represented in Figure 4, called, respectively, Segments 1, 2, 3, from the numbers at the upper plane of each segment. Each of these planes is represented by an irregular figure, (B, C, D, E, Fig. 4), resembling a triangle whose sides are formed by the endocardium of the right and left ventricles, and whose apex is the upper end of the fibrous auriculoventricular septum.

The original block at the upper portion of the plate shows the endocardial surface of the left ventricle, and the irregular nodules of calcareous material are well indicated as projecting out into the cavity of the left ventricle, and causing irregular projections of the endocardium. It can also be noted that the calcareous material really forms an irregular column which runs from right to left just where the auriculoventricular fibrous septum joins the ventricular septum forming a groove for the bundle of His, and this can be verified by examining the segments of the original block by means of a small hand lens. This appearance is indicated by Sections B, C, D, E in Figure 4, which show cross-sections of the ventricular septum ending in the apex formed by the fibrous auriculoventricular septum. At *a* in Figure 4, B, the bundle of His is seen branching from each ventricle, the long strip *b* forming the branch for the left ventricle. This is just beneath the endocarium, while the branch for the right ventricle *c* is deeper down beneath the surface of the right ventricle. Although this portion of the bundle is farthest away from the calcareous nodule at the base of the mitral valve (Fig. 3, B), yet the column of calcareous material has extended along the course of the bundle as far as this point, and a small point

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Fig. 6.—To the left of the picture is seen the fibrous auricular septum branching into the auriculo-ventricular fibrous septum. Below this, in about the center of the picture is the small yellow band of muscle fibers of the bundle of His. Above this bundle and to the right of it, almost completely surrounding it is the calcareous nodule pressing on it in several directions. Beyond this to the right is the normal heart muscle. These sections were made from Segment C, Figure 4. (Dr. T. M. Wright.)

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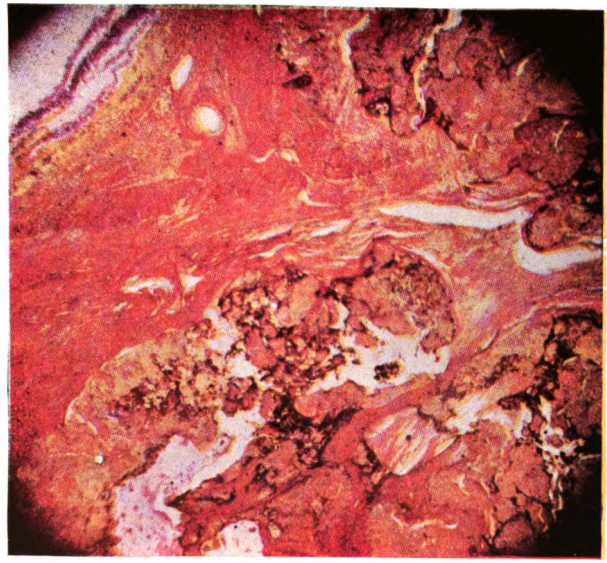

Fig. 7.—To the left and above is the red connective tissue of the fibrous ring, and in the center of the picture is the small atrophic band of yellow muscle fibers of the bundle of His. It is surrounded on all sides by calcareous material and also shows marked fibrous myocarditis, as indicated by the red bands of connective tissue. This section was made from the Segment D, Figure 4. (Dr. T. M. Wright.)

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of this material can be seen at D. This touches the upper part of the left branch, but probably this did not exert any pressure on the bundle of His at this point, whereas the deposit nearer the original source of the calcareous material not only pressed on the bundle, but apparently in places almost entirely replaced it.

The direction and situation of Segment 2 (Fig. 4, A) is indicated in the original block labeled natural size by the dotted lines marked 2-2. On viewing this on cross-section as C, Figure 4, a small nodule is seen to the right and below the bundle, but in Segment 3 (Fig. 4, D) the entire region of the bundle of His at *a* is involved in the deposit of lime salts. The plane of this section is seen at the dotted lines 3-3 in the original blocks.

In E, Figure 4, the mass of lime salts is even larger, and in both of these situations it will be seen from future studies of microscopic sections that the pressure exerted by the deposits produced atrophy, fibrosis and in one place almost a complete obliteration of the bundle of His. This plate (Fig. 4) in itself shows very clearly how the lesion must have interfered with the normal course of impulses from the auricles to the ventricles.

DESCRIPTION OF MICROSCOPIC SECTIONS.

Serial sections were cut from three different places in each of these segments. Figure 4, B, C, D, E, show the plane representing the directions of the sections and they can be seen, therefore, to pass through the junction of the upper part of the interventricular septum with the annulus fibrosus or fibrous ring between the auricles and ventricles. Since the bundle of His passes directly through this junction, transverse sections were made through the bundle of His throughout its entire extent until the bundle branched for the right and left ventricles; oblique and longitudinal sections were, of course, made through this latter area of branching.

Section D (Fig. 4) was made from Segment 3 at a point farthest from the branching of the bundle and nearest, therefore, to Point B seen in Figure 3, the photograph of the gross specimen.

The entire area occupied by the bundle of His was infiltrated by a calcareous material, a portion of which stained blue with hematoxylin. At first sight it would appear that the entire bundle of His had been obliterated, but on closer inspection there was found a narrow strip of muscular tissue surrounded on all sides by calcareous infiltration or newly formed fibrous tissue.

This mass was about 0.05 of an inch long and about 0.01 of an inch in width as measured by the micrometer scale, whereas the normal bundle is 0.1 of an inch in diameter.

In other sections from this same segment the strip measured only 0.03 of an inch in length, but was apparent in all sections from this end of the segment.

A second set of sections was cut from the middle portion of this segment, No. 3, and in some of these sections the bundle showed great atrophy. This measured 0.04 of an inch in longitudinal direction, but was 0.025 of an inch in cross diameter. It contained a few strips of newly formed fibrous tissue, showing typical fibrous myocarditis.

In other sections cut from this part of Segment 3 the thin strip of the bundle of His appeared in about the center of the calcareous area; it was 0.05 of an inch in length and 0.02 of an inch in thickness. In other sections cut from this same block the bundle of His at first sight seemed to have entirely disappeared, but on further examination small groups of cells were found which seemed to be mere remnants of the atrophic bundle of His. Many of these resembled connective-tissue cells, while others, when examined with the immersion

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lens, showed the large nucleus of the heart-muscle fiber surrounded by the fibrillar protoplasm of the heart muscle.

In the sections from that part of Segment 3 nearest to the branches to the ventricles the thin strip of the bundle of His measured 0.07 of an inch in length and 0.02 of an inch in width; in other sections from this same area the bundle only remained as thin atrophic bands of muscle fibers surrounded by thick strands of connective tissue. These muscle fibers had almost completely lost their cross-striations, but were probably able to preserve the continuity of the bundle.

In Segment C, Figure 4, cut as the central block of the three portions, into which the original block of segments was divided, somewhat different conditions were noted. In sections taken from that portion of the block furthest away from the branching of the bundle of His for the ventricles the calcareous infiltration around the bundle of His was much smaller in area, and it had not invaded the bundle. One small calcareous mass was found on either side of the bundle between the fibrous tissue capsule and the endocardium of the right and left ventricle respectively. The bundle itself is surrounded by a thick connective tissue, sending numerous branches in between the muscular bundles themselves. The bundle in this region measured 0.02 of an inch in the direction from the auricle to the ventricle or from base to apex; in the direction from the right to the left ventricle it measured 0.08 of an inch.

In sections which were made from the middle of Segment 2 the bundle measured 0.03 of an inch from apex to base and 0.08 of an inch from ventricle to ventricle. There were two small calcareous areas in the connective tissue surrounding the bundle and a very small one in the fibrous auriculoventricular septum, but there was no evidence of pressure on the bundle itself by these masses.

In sections made from that part of Segment 2 nearest the branching of the bundle for the ventricles, the bundle of His again became smaller, while the calcareous deposits were much larger; in places these had entirely replaced the connective-tissue capsule which separated the bundle from the ventricular septum. They had even invaded the bundle at its periphery and they must have produced pressure on this structure; the bundle measured 0.015 of an inch in a direction from base toward apex and 0.06 of an inch in a direction from ventricle to ventricle. In other sections from this same area the atrophy of the bundle was even more pronounced, for it measured only 0.01 of an inch from base to apex. The changes in the bundle of His itself which were seen when examined under the high power were certainly produced by the pressure of the calcareous material on the bundle; this had produced chronic fibrous myocarditis. When examined by Van Giesen's stain, both large and small bands of fibrous tissue were seen traversing the bundle. The muscular fibers of the bundle were narrower than normal, measuring about 0.0003 of an inch, while the muscular fibers of the regular heart muscle measures 0.001 of an inch in breadth.

The arteries in the bundle of His showed marked endarteritis; the calcareous material surrounding the bundle was typical, and this was surrounded by a thick fibrous capsule with very few fibroblasts, but in certain areas there were numerous densely packed fibroblasts forming small groups; in places these were more loosely packed, giving the tissue a myxomatous appearance.

In certain portions of the bundle made from Segment 2 there were groups of fibroblasts and a few fat cells. The smaller strands of connective tissue could often be seen surrounding individual muscle fibers producing marked atrophy.

The sections from Segment 1 showed the bundle after it had branched from the right and left ventricle; these branches showed some fibrous myocarditis and a newly formed fibrous tissue at times containing fine granular deposits of lime

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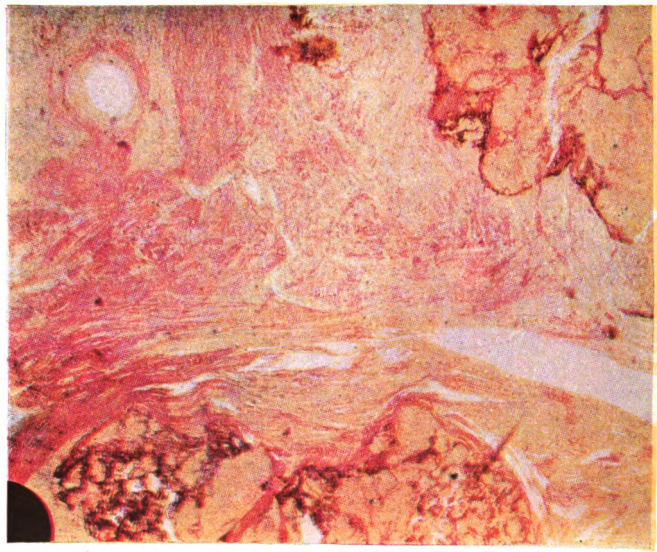

Fig. 8.—This shows the bundle of His in the center of the picture as yellow muscle fibers. It is invaded by the red bands of connective tissue, and surrounded on all sides by calcareous material. (Dr. T. M. Wright.)

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salts. The perinuclear spaces of the muscle fibers showed numerous fine light brown granules characteristic of brown atrophy.

GENERAL CONDITION OF HEART MUSCLE.

Sections were examined from several portions of both auricles and ventricles, but with the exception of marked brown atrophy and shriveling of the nuclei of the heart muscle no other changes were noticed. Sections from the coronary artery or its branches showed marked chronic fibrous endarteritis, in places the intima being twice as thick as the media. Whether the death of the patient was produced by the disease in the bundle of His or by coronary artery disease or both is difficult to say.

CONCLUSIONS.

From what has been said it can be seen that the primary lesion in this case consisted in marked calcareous infiltration of the auriculoventricular groove and its surrounding muscular and fibrous tissue. This produced pressure on the bundle of His, causing extensive fibrous myocarditis with atrophy of the muscular fibers. These conditions must have interfered with the normal transmission of the muscular impulse from the auricles to the ventricles, thus producing the symptoms described in the paper.

We desire to thank Drs. Retzer and Hirschfelder for their interest in this case, and Prof. T. W. Simon and Dr. T. M. Wright for the color photographs illustrating this article.

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PROCEEDINGS OF THE SESSION

TUESDAY, JUNE 2.—AFTERNOON.

The Section was called to order at 2 p. m. in the First Regiment Armory by the Chairman, Dr. W. B. Cannon, Boston.

Dr. Coplin offered a resolution that the delegate of the Section be instructed to submit to the House of Delegates a request that the title of the Section be changed to the Section on Pathology, Anatomy and Physiology, and that the term "anatomy" be dropped from the title of the Section on Surgery and Anatomy. He stated that this was the wish of the Section on Surgery and Anatomy.

Several members spoke in opposition to the resolution and on motion of Dr. Winfield S. Hall, Chicago, the Section's delegate was instructed to oppose the question in the House of Delegates.

The Chairman read his address, entitled "The Opposition to Experimental Medicine."

Dr. Herman M. Adler, Boston, read a paper entitled "Experiments Toward a Physiologically Isotonic Solution of Salts."

Dr. H. Gideon Wells, Chicago, read a paper on "Chloroform Necrosis of the Liver." Discussed by Drs. O'Connell; R. E. Le Count, Chicago; Edward A. Schäfer, Edinburgh; V. C. Vaughan, Ann Arbor, Mich.; Louis B. Wilson, Rochester, Minn.; and H. G. Wells, Chicago.

A paper on "Safeguards of the Heart," was read by Dr. Henry Sewall, Denver.

Dr. Edward A. Schäfer, Edinburgh, Scotland, read a paper on "The Pitutiary Body." Discussed by Drs. A. J. Carlson, Chicago; R. E. Le Count, Chicago; Sawyer; F. C. Busch, Buffalo, N. Y.; and E. A. Schäfer, Edinburgh.

WEDNESDAY, JUNE 3.—MORNING.

The Section was called to order at 9 a. m.

Dr. D. H. Bergey, Philadelphia, read a paper on "Anaphylaxis Induced by Bacterial Proteids." Discussed by Drs. V. C. Vaughan, Ann Arbor, Mich.; and D. H. Bergey, Philadelphia.

A paper on "The Cleavage of Bacterial Proteids by Exposure to Direct Sunlight," was read by Dr. Victor C. Vaughan, Ann Arbor. Discussed by Drs. C. C. Guthrie, St. Louis; Martin H. Fischer, Livermore, Cal.; Parsons; McConnell; and V. C. Vaughan, Ann Arbor.

Dr. A. P. Ohlmacher, Detroit, presented a paper on "Therapeutic Immunization in Mixed Infections."

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The next paper was "Serum Diagnosis of Syphilis," by Dr. William J. Butler, Chicago. Discussed by Drs. Karl Koessler, Vienna; and W. J. Butler, Chicago.

A paper on "Histoplasmosis: a Fatal Infectious Disease Resembling Kala-azar Found Among Natives of Tropical America," was read by Dr. Samuel T. Darling, Ancon, Canal Zone. Discussed by Drs. H. B. Ward, Nebraska; and S. T. Darling, Ancon, Canal Zone.

Dr. E. R. Le Count, Chicago, gave a "Demonstration of Diseased Conditions of the Appendix," in connection with a number of pathologic specimens.

Wednesday, June 3.—Afternoon.

The meeting was called to order at 2 p. m. by the Chairman of the Section on Practice of Medicine.

A joint meeting was held with the Section on Practice of Medicine, the six papers below constituting a symposium on typhoid fever.

Dr. Cannon announced as the Nominating Committee for the Section on Pathology and Physiology, Drs. Hall, Wesbrook and Bergey.

A paper on "The Channels of Infection and the Suppression of Typhoid Fever," was read by Dr. M. J. Rosenau, Washington, D. C.

Dr. Francis W. Peabody, Boston, read a paper on "The Value of Blood Cultures."

A paper on "Typhoid Bacillus Carriers," was read by Dr. William H. Park, New York.

Dr. David L. Edsall, Philadelphia, presented a paper on "Conditions Simulating Perforation in Typhoid Fever."

A paper on "The Metabolism of Typhoid Fever," was read by Dr. P. A. Shaffer, New York.

Dr. Thomas McCrae, Baltimore, read a paper entitled, "Treatment of Typhoid Fever."

These six papers were discussed by Drs. James M. Anders, Philadelphia; Lipston; Alexander Lambert, New York; M. J. Rosenau, Washington, D. C.; R. L. Jones, Nashville, Tenn.; Francis W. Peabody, Boston; Henry Albert, Iowa City, Iowa; Marks; William Litterer, Nashville; John A. Lichty, Pittsburg; D. L. Edsall, Philadelphia; Lawrence Litchfield, Pittsburg; H. B. Weaver, Asheville, N. C.; E. P. Joslin, Boston; W. S. Thayer, Baltimore; Henry B. Favill, Chicago; J. A. Witherspoon, Nashville; G. E. Munson, Springfield, Ill.; Baron; Bryan; Coffin; and Thomas McCrae, Baltimore.

Thursday, June 4.—Morning.

The Section convened at 9 a. m.

The nominating committee made the following report: President, Dr. M. J. Rosenau, Washington, D. C.; Secretary, Dr. H. Gideon Wells, Chicago; Delegate, Dr. H. A. Christian. These were unanimously elected.

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A paper entitled, "The Diuretic Action of Adrenalin and the Active Principles of the Pituitary Gland," was read by Dr. E. M. Houghton, Detroit.

Dr. F. C. Busch, Buffalo, read a paper on "Further Results in Suprarenal Transplantation." Discussed by Drs. W. M. L. Coplin, Philadelphia; H. G. Wells, Chicago; Fonda; A. J. Carlson, Chicago; W. B. Cannon, Boston; and F. C. Busch, Buffalo.

Dr. Martin H. Fischer, Livermore, Cal., presented a paper on "The Nature and Cause of Edema." Discussed by Drs. A. J. Carlson, Chicago; A. D. Hirschfeld, Baltimore; W. L. Welch, Baltimore; H. G. Wells, Chicago; W. B. Cannon, Boston; and Martin H. Fischer, Livermore, Cal.

Dr. A. J. Carlson, Chicago, gave a paper on "Some New Points in the Physiology of Lymph and Lymph Formation." Discussed by Drs. W. L. Welch, Baltimore; H. G. Wells, Chicago; and A. J. Carlson, Chicago.

A paper by Dr. Isabella C. Herb, Chicago, on "Experimental Mumps," was presented. Discussed by Drs. Thomas McCrae, Baltimore; and Isabella C. Herb, Chicago.

Dr. C. C. Guthrie, St. Louis, gave a paper, with lantern slides illustrating "Some Observations on: (a) Growth of Hen; (b) Egg Production; (c) Weight of Eggs; (d) Fertility of Eggs, and (e) Size of Chicks After Extirpation and Transplantation of Ovaries in Chickens."

A paper was presented by George T. Kemp, Urbana, Ill., on "Some New Statistics on Blood Plates, and Some New Practical Points on Counting Them."

Dr. J. Henry Schroeder, Cincinnati, read a paper on "The Alleged Urinary Manifestations of Disease of the Pancreas."

The Chairman announced as representatives of the Section to cooperate with the Association General Committee on Nomenclature and Classification of Diseases, Dr. Walter Bierring, Iowa, and Dr. W. M. L. Coplin, Pennsylvania.

Friday, June 5.—Morning.

The Section was called to order at 9 a. m. by the Chairman.

A paper entitled, "A Clinical and Pathologic Study of a Case of Stokes-Adams' Disease," by Drs. Harvey G. Beck and William Royal Stokes, Baltimore, was read by Dr. Price.

A paper on "Intracranial Pressure," by S. Burt Wolbach, Boston, was read.

Dr. Winfield S. Hall, Chicago, presented a paper on "The Influence of Diet on the Composition of the Chyle." Discussed by Drs. Perry P. Engle, Newton, Iowa; R. T. Woodyatt, Chicago; A. C. Tenney, Chicago; G. T. Kemp, Champaign, Ill.; H. G. Wells, Chicago; and W. S. Hall, Chicago.

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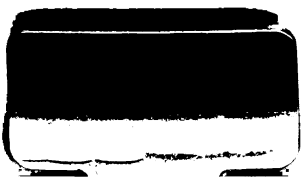

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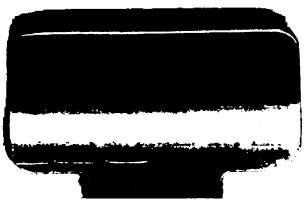

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